CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761194Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 30, 2021

To: Jenny Doan, BSN, MSN, PMP, Regulatory Project Manager
Division of Rare Diseases and Medical Genetics (DRDMG)

From: Adewale Adeleye, Pharm.D., MBA , Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for NEXVIAZYME (avalglucosidase alfa-ngpt)

BLA: 761194

In response to Division of Rare Diseases and Medical Genetics (DRDMG) consult request dated September 24, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original BLA submission for NEXVIAZYME (avalglucosidase alfa-ngpt) for injection, for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling available in SharePoint on July 26, 2021 at 1pm, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 21, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

21 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ADEWALE A ADELEYE
07/30/2021 03:50:57 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	July 23, 2021
Reviewer:	Catherine Lerro, PhD, MPH (Acting Team Lead) Division of Epidemiology I
Deputy Director:	CAPT. Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Avalglucosidase alfa (Nexviazyme)
Application Type/Number:	BLA 761194; IND 109569
Sponsor:	Sanofi Genzyme
OSE RCM #:	2020-1525

1. BACKGROUND INFORMATION

1.1. Medical Product

Avalglucosidase alfa (Nexviazyme, Sanofi Genzyme) is intended for the long-term enzyme replacement therapy (ERT) for treatment of patients with Pompe disease. Pompe disease is an autosomal recessive disease resulting in deficient activity of acid α-glucosidase (GAA), the enzyme needed to degrade glycogen in lysosomes (Sanofi 2020b). The recommended dosage for avalglucosidase alfa is 20 mg/kg or 40 mg/kg (of actual body weight) given every two weeks as an intravenous infusion for patients with late-onset Pompe disease (LOPD) (b) (4) Avalglucosidase alfa is available as lyophilized powder in a single-dose vial for reconstitution. The mean plasma elimination half-life in LOPD patients is 1.6 hours (Draft Label 2021).

Serious adverse reactions to avalglucosidase alfa include hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions (IARs). In clinical studies, 48% of treated patients experienced hypersensitivity reactions, including severe hypersensitivity (4%) and anaphylaxis (2%). IARs were reported in 34% of avalglucosidase patients in clinical studies. Ten severe IARs were reported; however, most IARs were mild to moderate. In a double-blind active-controlled trial, the most frequently reported adverse reactions in avalglucosidase alfa treated patients were headache, pruritus, nausea, urticaria, and fatigue. The safety profile of avalglucosidase alfa in pediatric patients 1 to 12 years old with Pompe disease was similar to the safety profile in older pediatric and adult patients with LOPD (Draft Label 2021).

As with all therapeutic proteins, there is a potential for immunogenicity. In the clinical trial program, patients with higher anti-drug antibody titers had increased incidence of IARs and hypersensitivity reactions. (b) (4)

1.2. Describe the Safety Concern

The Division of Rare Diseases and Medical Genetics (DRDMG) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for a broad-based signal detection study of avalglucosidase alfa during pregnancy.

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively (Dinatale 2016). The background risk of major birth defects and miscarriage for the indicated population is not well-characterized. Two small survey studies have evaluated pregnancy outcomes in women with Pompe disease, estimating risk of miscarriage to be between 12-18% in this population (Karabul, Berndt et al. 2014, Goker-Alpan, Kasturi et al. 2020). One of these studies evaluating 52 live births in women with LOPD reported a single case of congenital malformation (2%), specifically multi-cystic kidneys (Goker-Alpan, Kasturi et al. 2020). Pregnancy may cause worsening symptoms in women with Pompe disease (Draft Label 2021); as such these pregnancies should be considered high-risk and require additional monitoring (Karabul, Berndt et al. 2014).

During the clinical development program for avalglucosidase alfa (data cut-off date of November 13, 2020), five female patients in the treatment arm became pregnant (Baisden, Johnson et al. 2021). Two pregnancies resulted in live births, two in spontaneous abortions, and one is ongoing. No major birth defects were reported. Per protocol, avalglucosidase alfa treatment stopped when the pregnancy was identified (maximum one dose during the first trimester). Though there are no

published studies of avalglucosidase alfa and pregnancy, there were two published case reports describing other ERT use in pregnant women with adult-onset Pompe disease (Baisden, Johnson et al. 2021). These case reports did not provide evidence for ERT-related major birth defects or miscarriage.

In animal studies of reproductive toxicity conducted by the Sponsor, avalglucosidase alfa administered intravenously in pregnant mice resulted in maternal toxicity related to immunologic response (including an anaphylactoid response) and embryofetal loss. Avalglucosidase did not cross the placenta in mice, so the adverse effects were likely related to the immunologic response in the mothers. Embryofetal toxicity effects were not observed in pregnant rabbits (Sanofi 2020a).

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy and/or during lactation is recognized

☒ No approved indication, but use in women of child-bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† *If checked, please complete General ARIA Sufficiency Template.*

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☐ Electronic database study without chart review

☒ Other, please specify: Single-arm pregnancy safety study, which enrolls exposed pregnancies and/or lactating women into a protocol-driven observational cohort study for descriptive analyses and collects follow-up data, including detailed case narratives. These studies do not require inferential analyses and do not have the sample size requirements of a traditional pregnancy registry. A single-arm pregnancy safety study is appropriate because this drug is indicated for a rare disease, labeling advises about potential risks in pregnancy due to developmental toxicity in animal data, and thus a study sufficiently powered for a comparative analysis is not required.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population: ARIA lacks the capacity to identify lactating women.

Outcomes: ARIA lacks access to detailed narratives. The study being considered for broad-based surveillance is descriptive, without sample size requirements or a comparison group. Thus, detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and assess causality.

Covariates: ARIA does not have detailed information on potential confounders. The single arm safety study being considered would collect detailed narratives with information on potential covariates such as severity of Pompe disease, family history of the disease or outcomes, and lifestyle factors such as prenatal supplement use.

Analytical Tools: ARIA data mining methods have not been fully tested and implemented in post-marketing surveillance of maternal and fetal outcomes,

2.5. Please include the proposed PMR language in the approval letter.

DRDMG requests a PMR related to pregnancy outcomes; the proposed language as of July 22, 2021 is as follows:

> "Conduct a worldwide, descriptive safety study that collects data in women and their offspring who are exposed to Nexviazyme (avalglucosidase alfa-ngpt) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Outcomes of exposed infants, including growth and development, will be assessed through at least the first year of life. The study will collect information for 10 years.
>
> Draft Protocol Submission: 02/2022
> Final Protocol Submission: 10/2022
> Study Completion: 10/2032
> Final Report Submission: 04/2033"

The finalized PMR language will be issued upon approval.

3. References

Alglucosidase Alfa (Nexviazyme) Draft Label as of July 15, 2021, accessed July 23, 2021.

Baisden, K, T Johnson and LP Yao, 2021, Division of Pediatric and Maternal Health Memorandum: Nexviazyme (avalglucosidase alfa): Reference ID: 4748711.

Dinatale, M, Division of Pediatric and Maternal Health, FDA, The pregnancy and lactation labeling rule (PLLR), accessed May 19, 2020, from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf.

Goker-Alpan, O, VG Kasturi, MK Sohi, RP Limgala, SL Austin, T Jennelle, M Banikazemi and PS Kishnani, 2020, Pregnancy Outcomes in Late Onset Pompe Disease, Life (Basel), 10(9).

Karabul, N, J Berndt, C Kornblum, RA Kley, S Wenninger, N Tiling, E Mengel, U Plöckinger, M Vorgerd, M Deschauer, B Schoser and F Hanisch, 2014, Pregnancy and delivery in women with Pompe disease, Mol Genet Metab, 112(2): 148-153.

Sanofi, 2020a, 2.4 Nonclinical Overview, Original BLA Submission, Avalglucosidase alfa (neoGAA, GZ402666), BLA 761194.

Sanofi, 2020b, 2.5 Clinical Overview (Pompe Disease), Original BLA Submission Avalglucosidase alfa (GZ402666), BLA 761194.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CATHERINE C LERRO
07/23/2021 11:50:21 AM

SUKHMINDER K SANDHU
07/23/2021 11:51:33 AM

JUDITH W ZANDER
07/23/2021 11:53:24 AM

SARAH K DUTCHER
07/23/2021 11:56:25 AM

ROBERT BALL
07/23/2021 11:58:27 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 1, 2021
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761194
Product Name and Strength:	Nexviazyme (avalglucosidase alfa- ngpt) for injection, 100 mg/vial
Applicant/Sponsor Name:	Sanofi Genzyme
OSE RCM #:	2020-1526-2
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 21, 2021 for Nexviazyme. Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container label and carton labeling for Nexviazyme (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We find the container label and carton acceptable from a medication error perspective. We have no further comments at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Abraham, S. Label and Labeling Review for Nexviazyme (BLA 761194). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 12. RCM No.: 2020-1526-1

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
06/01/2021 03:20:00 PM

IDALIA E RYCHLIK
06/01/2021 03:42:44 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 12, 2021
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761194
Product Name and Strength:	Nexviazyme (avalglucosidase alfa-xxxx) for injection, 100 mg/vial
Applicant/Sponsor Name:	Sanofi Genzyme
OSE RCM #:	2020-1526-1
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 31, 2021 for Nexviazyme. Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container label and carton labeling for Nexviazyme (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We find the container label and carton unacceptable from a medication error perspective. We provide our recommendations below in Section 3.0 for Sanofi Genzyme.

[a] Abraham, S. Label and Labeling Review for Nexviazyme (BLA 761194). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 15. RCM No.: 2020-1526

3.0 CARTON LABELING AND CONTAINER LABEL RECOMMENDATIONS FOR SANOFI GENZYME

A. Container label and Carton Labeling
   1. To improve accuracy, revise the route of administration statement to read as follows: "For Intravenous Infusion after Reconstitution and Dilution." Consider boxing the statement to increase prominence in the event that font size must be adjusted due to space limitations.

B. Vial Container Label
   1. The primary display panel should be reserved for only the most important of product information (i.e. product name, strength and route of administration); relocate the storage statement to the side panel to not detract from more important product information.

C. Carton Labeling
   1. The manufacturer's name is identified on the PDP. PDP is reserved for the most important information. Other less important statements should be on the side panel. Relocate the manufacturer's name to the side panel.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
04/13/2021 09:44:34 AM

IDALIA E RYCHLIK
04/13/2021 10:11:02 AM

Clinical Inspection Summary Report

Date	March 17, 2021
From	Zana Marks, M.D., M.P.H. Karen Bleich, M.D. Kassa Ayalew, M.D., M.P.H. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Ann Punnoose, M.D. Linda Jeng, M.D Jenny Doan, RPM Division of Rare Diseases and Medical Genetics (DRDMG) Office of New Drugs (OND)
BLA #	761194
Applicant	Genzyme Corporation
Drug	Nexviazyme (Avalglucosidase alfa)
NME (Yes/No)	Yes
Therapeutic Classification	Enzyme replacement therapy
Proposed Indication	Enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (acid a-glucosidase deficiency)
Consultation Date	December 1, 2020
Review Priority	Priority
Summary Goal Date	March 19, 2021
Action Goal Date	May 18, 2021
PDUFA Date	May 18, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two trials, Study EFC14028 and Study ACT14132, were submitted to the Agency in support of a new Biologics License Application (BLA 761194) for the use of avalglucosidase alfa for the treatment of patients with Pompe disease. Five clinical investigators who participated in Study EFC14028 were selected for inspection: Dr. Joel Charrow [Site 8400023], Dr. Paula Clemens [Site 8400025], Dr. Tahseen Mozaffar [Site 8400011], Dr. Sergey Illarioshkin [Site 6430001] and Dr. Priya Kishnani [Site 8400006]. Two clinical investigators who participated in Study ACT14132 were additionally chosen for inspection: Dr. Priya Kishnani [Site 8400001] and Dr. David Kronn [Site 8400002].

For Study EFC14028, the inspection of Dr. Charrow identified a data discrepancy regarding a protocol violation for the use of protocol prohibited methotrexate, rituximab, immunoglobulins and other immunosuppressants involving all three subjects enrolled at the study site. The submitted protocol deviation data listings include the protocol violation for

all three subjects; however, according to the records at the site, and according to the CRFs submitted by the sponsor, none of the three subjects at the site had taken the prohibited medications.

The inspection of Dr. Charrow additionally found that spirometry results at baseline and Week 49 for Subject (b) (6) were available at the site but omitted from the submitted data listings. This subject was in the study drug arm of the study. The primary endpoint for this subject (change in FVC (% predicted) from baseline to Week 49) was a decrease of 6.7. The subject was omitted from the per-protocol population of the study because the Week 49 spirometry was obtained out of window at Week 53.

OSI recommends that DRDMG request clarification from the sponsor regarding the discrepancy between the submitted prohibited medication protocol violation data and the CRF data identified during the inspection of Dr. Charrow, and additionally request information about any other instances of discrepancy between the submitted protocol violation data and the CFR data. Other than the data discrepancies described, the clinical data generated by the inspected investigators appear reliable. No significant study conduct issues or regulatory violations were identified at any of the inspected entities.

II. BACKGROUND

Avalglucosidase alfa is an enzyme replacement therapy proposed for the treatment of patients with Pompe Disease, a chronic and life-threatening disease cause by a deficiency of the enzyme acid alpha-glucosidase (GAA). The Applicant submitted clinical data from two trials in support of the use of avalglucosidase alfa for patients with late-onset Pompe disease (Study EFC14028) and for infantile-onset Pompe disease (Study ACT14132).

Study EFC14028
Study EFC14028 is a phase 3, randomized, double-blind, comparator-controlled study comparing avalglucosidase alfa to standard of care alglucosidase alfa in treatment naïve patients with late-onset Pompe disease (LOPD).

The primary objective of the study is to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength. The primary efficacy endpoint is the change in forced vital capacity (FVC)% predicted in the upright position from baseline to 12 months (Week 49). Secondary endpoint assessments include the 6-minute walk test (GMWT), hand-held dynamometer (HHD) lower extremity strength, and the quick motor function test (QMFT).

The study includes a blinded primary analysis period (PAP) followed by an open-label extended treatment period (ETP). In the PAP portion of the study, eligible subjects were randomized 1:1 to receive the study drug or treatment with the active comparator for 49 weeks. The dosing regimen for each treatment arm was 20 mg/kg administered IV every

other week, for a total of 25 doses. At the end of the PAP, subjects in the alglucosidase alfa arm were switched to treatment with avalglucosidase alfa.

100 subjects were enrolled into the study at 55 study sites in 26 countries. The data cutoff date for the submitted interim analysis is March 19, 2020.

Study ACT14132

Study ACT14132 is a phase 2, open-label, ascending dose cohort study in pediatric patients with infantile-onset Pompe disease who were previously treated with alglucosidase alfa and demonstrated clinical decline or sub-optimal clinical response.

The primary objective of the study is to evaluate the safety profile of avalglucosidase alfa and the primary endpoints are assessments of adverse events. The key secondary efficacy endpoints include the change in the following parameters at 6 months: Gross Motor Function Measure-88 (GMFM-88), Quick Motor Function Test (QMFT), and Pompe Pediatric Evaluation of Disability Inventory (Pompe-PEDI).

Stage 1 of the study enrolled subjects with clinical decline into one of two ascending dose cohorts: subjects enrolled into cohort 1 received avalglucosidase alfa at 20 mg/kg every other week; subjects in cohort 2 received avalglucosidase at 40 mg/kg every other week for 6 months.

In Stage 2 of the study, subjects with sub-optimal clinical response were enrolled into cohort 3 in which they were randomized 1:1 to receive either avalglucosidase alfa 40 mg/kg every other week or their current stable dose of alglucosidase alfa for 6 months.

After the 6-month treatment period, subjects had the option to continue long term avalglucosidase alfa treatment and follow-up in the Extension Period for up to a total of 3 years in the study. Cohort 3 subjects who had been randomized to receive alglucosidase alfa could switch to treatment with avalglucosidase alfa or discontinue the study.

22 subjects were enrolled into the study at 10 study sites. The data cutoff date for the submitted interim analysis is September 30, 2019.

III. RESULTS

1. Paula Clemens, M.D.
Site 8400025, Study EFC14028
200 Lothrop Street
University of Pittsburgh
Pittsburgh, PA 15213

Dr. Clemens was inspected from January 25 -29, 2021 as a data audit for Study EFC14028. This was the first FDA clinical inspection of the investigator.

Dr. Clemens enrolled four adult subjects into Study EFC14028, including 1 subject assigned to the avalglucosidase alfa arm and 3 to the active comparator (alglucosidase alfa) arm. All four subjects completed the blinded phase of the study and are now in long term open-label follow-up.

All subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. The reviewed records included the informed consent forms, inclusion/exclusion criteria, randomization scheme, primary endpoint data, adverse events, protocol deviations, laboratory tests, and electronic case report forms (CRFs). Blinding procedures were reviewed. Regulatory documentation was also examined, including the Institutional Review Board (IRB) approvals of the study protocol and amendments, signed investigator agreements (Form FDA 1572s), delegation of duties log, financial disclosures, site training records, investigator's reporting to sponsor, monitoring records, and investigational drug storage and accountability records.

Due to Covid-19 hospital restrictions regarding room ventilation, there was an interruption in PFT testing at the site from June through December of 2020. PFT testing resumed after the installation of a negative air pressure hood in the unit where subjects were evaluated and treated. Records at the site document that the PFT testing interruption was discussed with the sponsor and reported to the IRB.

Reviewer comment: The COVID-related PFT testing interruption at the site occurred after the data cut-off date for the interim report (March 19, 2020) and thus would not affect data submitted to the agency. Primary endpoint PFT testing at Week 49 was performed for the 4 subjects at the site prior to the PFT interruption at the site. There is no evidence of harm to subjects related to the PFT testing interruption. The impact of COVID-19 on the study is discussed in the CSR.

The protocol required efficacy and safety assessments were performed adequately. No unreported protocol deviations or adverse events were identified during the inspection.

The primary efficacy endpoint measurements for the FVC values (% predicted) at baseline and Week 49 were verified for all subjects by comparing the submitted data listings to the source records at the site. The secondary endpoint 6MWT (6-minute walk test) values were also verified for all study subjects.

There were no significant regulatory violations in study conduct and no Form FDA 483 Inspectional Observations was issued.

2. Joel Charrow, M.D.
Site 8400023, Study EFC14028
225 E. Chicago Ave Box #59
Ann and Robert H. Lurie Children's Hospital of Chicago
Chicago, Il 60611

Dr. Charrow was inspected from January 14-19, 2021 as a data audit for Study EFC14028. This was the first FDA clinical inspection of the investigator.

Dr. Charrow enrolled three adult subjects into Study EFC14028, including 1 subject assigned to the avalglucosidase alfa arm and 2 to the active comparator (alglucosidase alfa) arm. All three subjects completed the blinded phase of the study and are now in long term open-label follow-up.

All three subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. The reviewed records included the informed consent forms, subject medical records (including inclusion/exclusion criteria, randomization scheme, primary endpoint data, adverse events, laboratory tests), and electronic case report forms (CRFs). Regulatory documentation was also examined, including the Institutional Review Board (IRB) approvals of the study protocol and amendments, signed investigator agreements (Form FDA 1572s), delegation of duties log, financial disclosures, training and study blinding procedures, investigator's reporting to sponsor, monitoring records, and investigational drug storage and accountability records.

Data discrepancies were identified between the data listings for protocol deviations at the site and the source records at the site. The discrepancies involved the presence of deviations in the data listings that did not appear to have occurred according to site records and site staff. Specifically, according to the line listings for protocol deviations, all subjects at the site have the following protocol deviation: "protocol prohibited methotrexate, nituximab, immunoglobulins and other immunosuppressants administered after the screening." According to site records and staff, none of the subjects at the site had taken these medications after screening. Additionally, the data listing for protocol deviations stated that the ECG was not performed for Subject (b) (6) Source records at the site indicated that all ECGs required by the protocol was completed for this subject. There were no unreported protocol violations identified during the inspection.

Reviewer comment: OSI reviewed the CRFs for the three subjects at Dr. Charrow's site which were submitted to the application upon request. No prohibited immunosuppressant medications are listed for the subjects. The prohibited concomitant medication protocol deviation was thus not entered into the CRF by Dr. Charrow or site staff. We recommend that DRDMG sends an information request to the sponsor requesting an explanation for

the inclusion of the prohibited concomitant medication protocol deviation in the line listings that are not included in the CRFs and for clarification as to the veracity of the prohibited concomitant medication protocol deviation listed for other subjects in the trial.

There was one data discrepancy regarding concomitant medications in which the medication recorded in the source records was not included in the data listings. According to the source records, Subject (b) (6) received amitriptyline for depression from (b) (6)

Reviewer comment: The baseline visit date for Subject (b) (6) The subject stopped the medication shortly after starting the study. While the use of concomitant medication (amitriptyline) should have been reported, the isolated finding is unlikely to have affected either subject safety, efficacy and safety analyses.

There was a grade 1 adverse event for Subject (b) (6) (acid reflux) which was missing from the data listings because it was entered into the EDC after the data cutoff date. No additional adverse events that occurred prior to the data cutoff date were absent from the data listings.

Reviewer comment: The adverse event of acid reflux was entered into the EDC several months after its occurrence. Given that the AE was mild and resolved, there is no evidence of subject harm. There were no additional instances of missing adverse events that occurred prior to the data cutoff date.Thus there is no data reliability concern regarding adverse event reporting.

The source records for the primary endpoint measurements for the FVC values (% predicted) at baseline and Week 49 were reviewed for all subjects at the site. Discrepant values for the primary endpoint were identified between the source spirometry result and the data in the data listing for Subject # (b) (6). Additionally, the primary endpoint results were absent from the submitted data for Subject # (b) (6) but present in the source records at the site. These data discrepancies are summarized in Table 1.

Table 1: Primary endpoint data discrepancies

Subject ID Study Arm	Visit Date	FVC (% predicted, upright)	
		Source spirometry report	Applicant's data listing
(b) (6) Control arm (Alglucosidase)	Baseline (b) (6)	44.3	42.596
	Week 49 (b) (6)	45.4	44.444
	Primary endpoint (change from baseline)	1.1	1.8484
(b) (6)	Baseline	62.8	---

Avalglucosidase arm	(b) (6)		
	Week 49 (b) (6)	56.1	---
	Primary endpoint (change from baseline)	-6.7	---

Reviewer comments: The pulmonary function test values are sent to the sponsor from ERT and are not entered by site staff into the CRF. The discrepant results for Subject (b) (6) (control arm of study) are of uncertain etiology, however, the difference is small and does not favor the study drug.

For Subject (b) (6) the Week 49 spirometry was done out of window at Week 53. Subject (b) (6) is included in the modified intent-to-treat population (mITT) but is excluded from the per-protocol population. The spirometry results for Subject (b) (6) should not have been omitted from the submission.

The inspection revealed no significant regulatory violations. No Form FDA 483, Inspectional Observations was issued to Dr. Charrow at the conclusion of this inspection.

3. David Kronn, M.D.
Site 8400002, Study ACT14132
503 Grasslands Road Suite 200
Regional Medical Genetics Center of New York
Valhalla, NY 10595

Dr. Kronn was inspected from January 19-26, 2021 as a data audit for Study ACT14132. This was the first FDA clinical inspection of the investigator.

Dr. Kronn enrolled five pediatric subjects into Study ACT14132, including 1 subject to Cohort 1 (avalglucosidase alfa 20mg/kg), 1 subject to Cohort 2 (avalglucosidase alfa 40mg/kg), and 3 subjects to the control arm of Cohort 3 (alglucosidase alfa). At the time of the inspection, the five subjects are in long-term follow-up.

All subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. The reviewed records included but were not limited to the informed consent forms, inclusion/exclusion criteria, randomization scheme, primary endpoint data, adverse events, laboratory tests, and electronic case report forms (CRFs). Regulatory documentation was also examined, including the Institutional Review Board (IRB) approvals of the study protocol and amendments, signed investigator agreements (Form FDA 1572s), delegation of duties log, financial disclosures, training procedures, investigator's reporting to sponsor, monitoring records, and investigational drug storage and accountability records.

The site reported an incident in which "black specks" were noted within four investigational product vials after reconstitution. The issue was reported to the sponsor

and resolved through changing the brand of syringe needles. No subjects received investigational product from the vial in question. A document at the site states that the vials were isolated and retrieved by the site monitor.

Reviewer comment: While the inspection scope did not include manufacturing or product quality, the records at the site indicate that the incident was appropriately handled in terms of isolating and returning the vials in question. The issue resolved after changing the syringe manufacturer used by the site. The IRB was not notified because no subjects received drug product from the vials in question.

Two subjects at the site, Subject #s (b) (6) were not appropriately re-consented when a new version of the consent form became available and was approved by the IRB on 7/15/2020. The new version of the consent form increased the length of time the investigational product could be received (from 2.5 years to up to 6.5 years) and increased the length of participation in the study (from 3 years to 7 years).

Reviewer comment: The new version of the consent form became available after the cutoff date for the current interim analysis and this version of the consent form was not included in the submission. While the subjects continue to receive the investigational product and should have been re-consented, the changes described between the consent documents appear minor and are unlikely to impact subject safety or participation decision.

The study endpoint tests Gross Motor Function Measure-88 (GMFM-88), Pompe-PEDI, and Quick Motor Function Test (QMFT) were administered by physical therapists at the site. The tests were subsequently scored by the sponsor. The site received a report from the sponsor containing the raw scores and a statistical report which the site then entered into the eCRF. Scores from the GMFM-88, Pompe-PEDI, and QMFT were compared with those reported in the data listing and in the eCRF for all subjects. Two discrepant endpoint values were identified as detailed in Table 2.

Table 2: Endpoint Data Discrepancies

Subject ID **Study Arm**	**Source record result**	**Submitted data listing result**
(b) (6)	Baseline Pompe PEDI raw score	
Cohort 3 Alglucosidase alfa	86	85
(b) (6)	Week 13 GMFM88	
Cohort 3 Alglucosidase alfa	137	136

Reviewer comment: The inspection of Dr. Kronn identified two endpoint data discrepancies. Both discrepancies were minimal (a Pompe PEDI result of 85 should have been 86; a GMFM88 score of 136 should have been 137) and unlikely to affect the data analysis. The endpoint data discrepancies are of uncertain etiology. In both cases, the magnitude of the difference between the source records and submitted subject line listings scores is small and unlikely to have a significant effect on the primary efficacy analyses.

There was no evidence of under-reporting of adverse events or protocol deviations.

The inspection revealed no significant regulatory violations. No Form FDA 483, Inspectional Observations was issued to Dr. Kronn at the conclusion of this inspection.

4. **Tahseen Mozaffar, M.D.**
Site 8400011, Study EFC14028
200 South Manchester Avenue, Suite 110
University of California Irvine
Orange, CA 92868

Dr. Mozaffar was inspected from December 14-17, 2020 as a data audit for Study EFC14028. This was the first FDA clinical inspection of the investigator.

Dr. Mozaffar enrolled three adult subjects into Study EFC14028, including 1 subject assigned to the avalglucosidase alfa arm and 2 to the active comparator (alglucosidase alfa) arm. All three subjects completed the blinded phase of the study. Subject # (b) (6) (avalglucosidase alfa arm) discontinued study participation due to an adverse event (myocardial infarction) on study day 677. The two other subjects at the site remain in long term open-label follow-up.

Documents reviewed during the inspection included IRB approvals, financial disclosure forms, training records, informed consent forms, pharmacy binders, and subject records. The three enrolled subjects' records and source documents, including concomitant medications, adverse events, treatment assignments, discontinuations, protocol deviations, and efficacy endpoints were compared against the line listing data to ensure data was reported accurately.

Discrepancies were identified between the investigational product shipment records and inventory records. Additionally, some of the logs of investigational product dispensation were missing. Documentation of investigational product preparation for subjects was available and no discrepancies were identified in the subject dosing records.

Reviewer comment: The issues with the investigational product records were reportedly attributed to staff turnover in the pharmacy. Despite the turnover, the records should have been in order and maintained as Dr. Mozaffar is responsible for the adequacy and retention of study documents. No discrepancies were identified in IP preparation records for subjects suggesting that despite the limits of the pharmacy documentation, subjects were appropriately dosed with IP during the study.

According to the protocol, infusion-associated reactions (IARs) were required to be reported to the sponsor within 24 hours of the event. Three IARs for Subject # (b) (6) (bilateral hand itching, bilateral itching on palms, and bottom lip burning sensation) were reported to the sponsor from 3 weeks – 11 weeks after occurrence.

Reviewer comment: The three IARs should have been reported to the sponsor within 24 hours, as required by the protocol. In all three instances of late reporting, the severity of the reaction was classified as mild and resolved same day, and all three instances are present in the AE data listing for the site. There is thus no evidence of subject harm or concerns regarding data reliability related to the failure to report the IARs within 24 hours.

The primary endpoint data was verified for all three subjects at the site. There was no evidence of under reporting of adverse events or protocol deviations.

The inspection revealed no significant regulatory violations. No Form FDA 483, Inspectional Observations was issued to Dr. Mozaffar at the conclusion of this inspection.

5. Priya Kishnani, M.D.
Site 8400006, Study EFC14028
Site 8400001, Study ACT14132
2301 Erwin Road, Room 7607
Duke University Medical Center
Durham, N.C. 27710

Dr. Kishnani was inspected from January 13-22, 2021 as a data audit for Study EFC14028 and Study ACT14132 This was the first FDA clinical inspection of the investigator.

For both Study EFC14028 and ACT14132, the inspection scope included review of informed consent forms, inclusion/exclusion criteria, randomization assignments (for Study EFC14028), primary endpoint data, adverse events, laboratory tests, and electronic case report forms (CRFs). Regulatory documentation was also examined, including the Institutional Review Board approvals of the study protocols and amendments, signed investigator agreements (Form FDA 1572s), delegation of duties logs, financial disclosures, site training, investigator's reporting to sponsor, sponsor's monitoring, and investigational drug storage and accountability records.

<u>Study EFC14028</u>
Dr. Kishnani enrolled one subject (Subject (b) (6)) into Study EFC14028, into the active comparator (alglucosidase alfa) arm. The other study subject at the site (Subject (b) (6), also in the alglucosidase alfa arm) transferred to the site on (b) (6), after having enrolled at a different site. At the time of the inspection, both subjects were in long term open-label follow-up.

The primary endpoint FVC values at baseline and Visit 27 were verified for both subjects. There was no underreporting of adverse events or protocol deviations. No regulatory violations were identified.

<u>Study ACT14132</u>

Dr. Kishnani enrolled three pediatric subjects into Study ACT14132. All three were enrolled into Cohort 3 and randomly assigned to the avalglucosidase alfa arm of the study. At the time of the inspection, all three subjects were in long term follow-up.

There were four adverse events for Subject (b) (6) in the source records that occurred prior to the data cutoff date and were not included in the data listings. The missing adverse events (fall, headache, infusion port de-accessed by accident, and enuresis) were all classified as mild, resolved, and not AEs of special interest. Several additional adverse events that occurred after the data cut-off date were identified at the same time and reported to the sponsor. The error occurred due to the discovery of additional adverse events for this subject during a retroactive search of study records.

Reviewer comment: There is no evidence of subject harm related to the late discovery of these adverse events for Subject (b) (6). *The AEs that occurred prior to the data cutoff date should have been included in the application but are unlikely to affect the safety review of the study drug. The discovery of the AEs was reported to the sponsor as a protocol deviation. As the discovery was made after the data cutoff date for the study, it is not included in the data listings.*

The values for the endpoint assessments for the GMFM-88, QMFT, and Pompe-PEDI tests were verified for all three subjects enrolled at the site.

The inspection revealed no significant regulatory violations. No Form FDA 483, Inspectional Observations was issued to Dr. Kishnani at the conclusion of this inspection.

6. Sergey Illarioshkin, M.D., Ph.D.
Site 6430001, Study EFC14028
Research Center of Neurology
80 Volokolamskoye Shosse
Moscow, NA 125367 Russia

A remote regulatory assessment of Dr. Illarioshkin regarding his participation in Study EFC14028 was conducted from 2/18/2021 – 3/2/2021. An onsite inspection was not possible due to travel restrictions caused by the COVID-19 pandemic. Dr. Illarioshkin has no prior inspection history with FDA.

Dr. Illarioshkin enrolled 6 subjects into Study EFC14028, including 4 assigned to the avalglucosidase alfa arm and 2 to the active comparator (alglucosidase alfa) arm. All 6 subjects completed the blinded phase of the study and remain in long term open-label follow-up.

Documents at the study site were uploaded to Box.com for review, including signed investigator agreements (Form FDA 1572s), delegation of duties log, screening and enrollment log, informed consent log, study protocols and amendments, investigational product accountability logs, monitoring visit logs, a listing of approvals and dates by local and national ethics committees and the regulatory authority, and financial disclosures.

Five of the 6 subjects at the site signed consent for the review of records for the assessment, as required in Russia for the review of subject data for this assessment. For those 5 subjects (Subjects # (b) (6), reviewed records through Box.com included consent forms, qualifying medical history, physical exams, screening laboratory records, dosing records, adverse events, and efficacy endpoints.

Meetings with site staff were held via Webex conference calls with a translator provided by the sponsor. Procedures at the site including informed consent, maintenance of the study blind, staff training, investigational product control, and data management were reviewed with Dr. Illarioshkin and the site staff.

There were no discrepancies involving the primary endpoint FVC values for the five subjects who consented to the regulatory assessment. Review of the secondary endpoints identified a transcription error involving the abduction and adduction measurement fields used to calculate the hand-held dynamometry (HHD) lower extremity strength for Subject # (b) (6) The abduction and adduction fields are components of the 12-component score for the HHD lower extremity strength endpoint. The submitted and correct component scores are shown in Table 3. No data discrepancies were identified for the 6-minute walking test or quick motor function test endpoint results.

Table 3: Secondary endpoint HHD lower extremity strength data discrepancy *(correct endpoint value shaded)*

Subject, Treatment arm	**Baseline HHD component score**		**Week 49 HHD component score** *(no discrepancy)*		**Endpoint result (change from baseline to Week 49)**	
(b) (6) Alglucosidase alfa	Source report	Submitted data listing	Source report	Submitted data listing	Calculated using corrected baseline value	Submitted data listing
	1264	1259	1804	1804	540	511

Reviewer comment: The correct endpoint value for the secondary endpoint HDD lower extremity strength for Subject (b) (6) *(in the control arm of the study) is 540,* an improvement from baseline that is greater than that reported in the submission (511), . *The abductor/adductor results were switched when entering the source data into the EDC apparently due to transcription error. Additionally, there was no evidence of the error having been repeated for the other 4 subjects reviewed. The data discrepancies do appear insignificant and are unlikely to impact the reliability of the study data or subject safety.*

No unreported adverse events or protocol deviations were identified. No significant study conduct concerns were identified in this remote regulatory assessment.

{See appended electronic signature page}

Zana Marks, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Documentation
Review Division /Division Director
Review Division/Medical Officer
Review Division /Medical Team Leader
Review Division /Project Manager
OSI/Office Director
OSI/DCCE/ Division Director
OSI/DCCE/GCPAB Chief
OSI/DCCE/GCPAB Team Leader

OSI/ GCP Program Analysts
OSI/Database Project Manager

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ZANA H MARKS
03/18/2021 05:56:44 PM

KAREN B BLEICH
03/18/2021 06:25:44 PM

KASSA AYALEW
03/19/2021 08:02:30 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 15, 2021
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761194
Product Name, Dosage Form, and Strength:	Nexviazyme (avalglucosidase alfa-xxxx) for injection, 100 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sanofi Genzyme
FDA Received Date:	September 18, 2020
OSE RCM #:	2020-1526
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

Genzyme Sanofi submitted BLA 761194 Nexviazyme (avalglucosidase alfa-xxxx) for injection, on September 18, 2020 as part 2 of 2 of a rolling submission. Nexviazyme (avalglucosidase alfa-xxxx) was granted a Breakthrough Therapy status for the treatment of patients with Pompe disease (acid α-glucosidase deficiency). The Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the proposed Nexviazyme prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E-NA
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

On September 18, 2020, Sanofi submitted their final proposed clinical and quality sections, draft labels and labeling as part 2 of 2 of the rolling submission for BLA 761194. Nexviazyme (avalglucosidase alfa-xxxx) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

On June 2, 2020, during our proprietary name evaluation under IND 109569 (DMEPA Review OSE#2019-36346386), we communicated to the sponsor that their proposed dose/frequency of 20 mg/kg every 2 weeks requires multiple vials to achieve one dose may be prone to medication dosing and administration errors.[a] For example, the dose for a 70 kg patient would

[a]Abraham,S. Proprietary Name Review for Nexviazyme (IND 109569). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 May 26. Panorama No.: 2019-36346386.

require 14 vials (dose of 1,400 mg). We recommended that Sanofi Genzyme take this into consideration when they develop their product.

In their September 18, 2020, BLA submission, they proposed a new dose/frequency of 40 mg/kg every other week in addition to their 20 mg/kg every other week dosing. We communicated our medication error concern to DRDMG and the Division issued an information request (IR) to the sponsor (See Appendix C). In their December 10, 2020, response to our IR, Sanofi stated that pediatric patients with Infantile-Onset Pompe Disease (IOPD) would require a range of 4 vials to 26 vials with a median of 9 vials to 10 vials at the recommended dose of 40 mg/kg. Adults and adolescent patients with Late Onset Pompe Disease (LOPD) would require 8 vials to 38 vials with a median of 13 vials to 16 vials at the recommended dose of 20 mg/kg.

In their March 5, 2021, response to our IR, Sanofi stated that the risk of medication error due to a miscalculation of the number of vials for avalglucosidase alfa is very limited and the handling of the preparation of the infusion with avalglucosidase alfa is improved compared to that of alglucosidase alfa. The total number of vials needed for the same dose in Pompe patients is reduced by 50% with avalglucosidase alfa use because each vial of avalglucosidase alfa product contains 100 mg of active product, while alglucosidase alfa contains 50 mg. As per the applicant, the overdose could lead to higher incidence of anti-drug antibodies and infusion-associated reactions and underdose could lead to impact on efficacy outcomes. During March 3, 2021 pre-Late Cycle meeting, clinical team agreed with the Sponsor's rationale.

We note the public health benefit of this product for treatment of Pompe disease as there are limited treatment options for this ultra-rare, genetic disease. We also note the favorable safety profile of Nexviazyme, with no death or drug related serious adverse events during the clinical evaluations. Taking into consideration the public health benefit associated with Nexviazyme we find the use of multiple number of vials to be administered to be acceptable in this specific case.

Below, we provide recommendations to optimize the PI, carton labeling and container labels to help mitigate the risk of medication errors associated with the preparation and administration of Nexviazyme. We identified some areas of concern for the proposed PI and the proposed carton and container label. We provide our recommendations below in Table 2 for the Division and Section 3.1 for Sanofi Genzyme.

Table 1. Identified Issues and Recommendations for Division of Rare Diseases and Medical Genetics (DRDMG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	Dosage and Administration (D&A) section of	The first statement is an incomplete sentence. The subject of the sentence, Nexviazyme, is	Revise the sentence to read, "Nexviazyme must be reconstituted and diluted prior to use."

Table 1. Identified Issues and Recommendations for Division of Rare Diseases and Medical Genetics (DRDMG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the highlights lacks clarity.	missing which may lead to confusion.	Additionally, consider the following formatting changes and reordering of information as shown below to improve readablility: Nexviazyme must be administered every other day as intravenous infusion. (2.2) <u>Patients with Late-Onset Pompe Disease (LOPD)</u> The recommended dose of TRADENAME is 20 mg/kg of body weight. (2.1) (b) (4)
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, Section 2.2 (Administration Instructions) is text heavy and burdensome to read.	Decreased readability and lack of prominence of administration information may lead to medication error.	To enhance accessibility of the D&A information, consider using a bulleted format for D&A information.
2.	Section 2.3 has multiple statements related to (b) (4)	(b) (4) statements can lead to confusion and wrong dose medication errors.	Remove (b) (4) from section 2.3.
3.	As currently presented, Step 1 in Section 2.3 outlines a lengthy formula for calculating the	Typically, the Full Prescribing Information is intended for healthcare providers, not for patients. Healthcare providers and physicians are familiar with	Remove the formula for calculating the number of vials from Section 2.3 (Step 1).

Table 1. Identified Issues and Recommendations for Division of Rare Diseases and Medical Genetics (DRDMG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	number of vials needed to calculate the dose.	how to calculate number of vial(s).	
4.	As currently presented Administration Instructions precede section 2.3 Reconstitution and Dilution Instructions.	The drug product has to be reconstituted and diluted before it can be administered to patients. It is important to have these instructions in an orderly format.	Rearrange the sections so that Reconstitution and Dilution Instructs precede the Administration Instructions.
5.	(b) (4)		
		The use of N/A in the infusion table may cause confusion as to the intended meaning.	
6.	The storage information of the reconstituted and/or diluted drug is stated at the end of the preparation, reconstitution, and administration steps in Section 2.3	Presenting important storage information to the reader in a text heavy format with decreased readability may lead to misinterpretation and improper storage of the product.	Relocate the storage information of reconstituted and/or diluted drug to a new section 2.4 under a subheading “Storage of the Reconstituted and/or Diluted Solution”.

Table 1. Identified Issues and Recommendations for Division of Rare Diseases and Medical Genetics (DRDMG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The storage of the reconstituted or diluted solution is repeated in Section 16 .	The storage of the reconstituted and/or diluted solution should be presented in Section 2.	Delete the repeated storage of the reconstituted or diluted solution in Section 16.

3.1 CARTON LABELING AND CONTAINER LABEL RECOMMENDATIONS FOR SANOFI GENZYME

A. General Comments
   1. Confirm there is no text on the ferrule and cap overseal of the vials.
   2. Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located
   3. As currently displayed, "Tradename" is used instead of the conditionally approved name, "Nexviazyme". Proposed proprietary name, Nexviazyme, found conditionally acceptable by DMEPA on December 3, 2020 under BLA 761194. Replace the "Tradename" with conditionally approved name, "Nexviazyme" on container label and carton labeling.
   4. The format for expiration date is undefined. The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors. Submit expiration date in the format that is stated below. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
   5. As currently presented, the NDC number is denoted by a placeholder (xxxxx-xxx-xx). We request the actual NDC numbers for the container label and carton labeling to determine if they are appropriate.

B. Vial Container Label
   1. The statement of dosage is missing. If space permits, consider adding statement of dosage as "Dosage: See Prescribing Information".

2. If space permits, consider adding the storage information to the side panel and read as "Must Refrigerate at 2 °C to 8 °C (36 °F to 46 °F)".
3. The manufacturer's name and address are identified on the PDP. PDP is reserved for the most important information. Other less important statements should be on the side panel. Relocate the manufacturer's name and address to the side panel.

C. Carton Labeling

1. Per 21 CFR 610.61(e), The following items shall appear on the label affixed to each package containing a product: The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words "No Preservative". Ensure that the statement "No Preservative" appears on the carton labeling
2. Revise the inactive ingredient list to appear in alphabetical order as follows:

   "Each vial contains 100 mg of avalglucosidase alfa-xxxx, glycine (200 mg), L-Histidine (10.7 mg), L-Histidine HCl monohydrate (6.5 mg), mannitol (200 mg), and polysorbate 80 (1 mg)."
3. Per 21 CFR 610.61, add the words "No U.S. standard of potency" to the carton labeling
4. Consider including reconstitution instructions and storage conditions for the reconstituted product: "After reconstitution with 10 mL of Sterile Water for Injection, USP the resultant concentration is 100 mg/10 mL (10 mg/mL). If not used immediately, the reconstituted product can be stored up to 24 hours when refrigerated at 2°C to 8°C (36° to 46°F)"
   This may allow for the removal of "See prescribing information (b) (4)
5. Consider revising the Statement of dosage from (b) (4) to read as follows: "Dosage: See Prescribing Information"
6. It is unclear where the machine-readable product identifier is located on the label. The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode.
   NDC: [insert NDC]
   SERIAL: [insert serial number]
   LOT: [insert lot number]
   EXP: [insert expiration date]
   We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

4 CONCLUSION

Our evaluation of the proposed Nexviazyme prescribing information(PI), container label, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 1 for the Division and Table 3 for Sanofi Genzyme. We ask that the Division convey our carton labeling and container label recommendation to Sanofi Genzyme so that recommendations are implemented prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Nexviazyme received on September 18, 2020 from Sanofi Genzyme.

Table 3. Relevant Product Information for Nexviazyme	
Initial Approval Date	N/A
Nonproprietary Name	avalglucosidase alfa-xxxx
Indication	long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).
Route of Administration	intravenous
Dosage Form	for injection
Strength	100 mg/vial
Dose and Frequency	Patients with Late-Onset Pompe Disease: The recommended dose is 20 mg/kg of body weight administered every other week. (b) (4) [redacted]
How Supplied	Supplied as a sterile, white to pale-yellow lyophilized powder in single-dose vials. 100 mg vial in a carton.
Storage	Refrigerate vials of TRADENAME at 2°C to 8°C (36°F to 46°F). Do not use TRADENAME after the expiration date on the vial. Reconstituted and diluted solutions of TRADENAME should be used without delay. If immediate use is not possible, the reconstituted product can be stored up to 24 hours when refrigerated at 2°C to 8°C (36°F to 46°F); diluted product can be stored up to 24 hours when refrigerated at 2°C to 8°C (36°F to 46°F) and up to 9 hours (b) (4) [redacted]

APPENDIX C. INFORMATION REQUEST:

Information request and responses from Genzyme Sanofi received on December 10, 2020:

AGENCY REQUEST FOR INFORMATION ITEM NO. 1:

In an effort to better understand the number of vials of avalglucosidase alfa need for patients with IOPD and LOPD at 20 mg/kg qow and 40 mg/kg qow dosing, provide the average weights and typical weight ranges for infants with IOPD and for children and adults with LOPD.

Sanofi response:

In study ACT14132, conducted in 22 children with IOPD, body weight ranged between 10 and 64 kg with a median in the 3 cohorts ranging between 20.5 and 24.5 kg. Real life data indicate that it is representative of the global IOPD population to be treated, who usually has a body weight comparable to the standard population (1, 2). Additional information found in the literature show a relatively large proportion of patients can be underweight (3) (as opposed to overweight, thus reducing the probability that a large number of vials are needed generally). Using the maximum recommended dose of 40 mg/kg, the number of vials to be used in these patients at each infusion would range between 4 and 26 (median 9 to 10).

In the 3 studies conducted in adults and adolescents with LOPD, body weight ranged between 38 and 139 kg with a median ranging between 62.9 kg and 77.4 kg depending on studies and groups. Real life data indicate that it is representative of the global LOPD population to be treated, who usually has a body weight comparable to the standard population (1, 4). Using the recommended dose of 20 mg/kg, the number of vials to be used in these patients at each infusion would range between 8 and 38 (median 13 to 16).

Each vial contains 100 mg of avalglucosidase alfa. The number of vials to be reconstituted for an infusion is based on the individual patient's weight and the recommended dose of 20 mg/kg or 40 mg/kg, and should be calculated as follows:

- Patient total dose (in mg) = patient weight (kg) x dose (mg/kg).
- Number of vials to reconstitute = patient dose (in mg) divided by 100 mg/vial. If the number of vials includes a fraction, it should be rounded up to the next whole number.

Clear and detailed directions to use are provided in the proposed Prescribing Information. Of note, each vial of avalglucosidase alfa product contains 100 mg of active product, while each vial of alglucosidase alfa product contains 50 mg. Therefore, the total number of vials needed for the same dose is reduced by 50% with avalglucosidase alfa use, potentially leading to improved handling of the preparation of the infusion.

Table 1 Pompe Disease Birth Incidence Sources

Author	Pub Year	Years of Data collection	Location	Pompe disease incidence per 100,000 live births	Study design	Pompe Cases (IO=Infant Onset; LO=Late-onset)
Martiniuk (8)	1998	1990's	United States	2.5	928	31 mutations found
Scott (9)	2013		WA state, US	3.6	111,544	4 classic LO; no infantile based on mutations
Prosser (6)	2018		United States	3.35	Modeling study	Screening 4 Million babies would detect 40 cases of IO Pompe disease, and identify 94 cases of LO
Burton (5)	2020	2014-2019	Illinois State, US	4.24	684,290 Infants	29 Pompe disease: 3 infantile; 26 late-onset

AGENCY REQUEST FOR INFORMATION ITEM NO. 2:

Provide the incidence of IOPD and LOPD in the United States.

Sanofi response:

The US data shows a birth incidence of about 4/100,000 live birth (both LOPD and IOPD) in the most recent and largest screening study, by Burton et al, in a cohort of 684,290 infants (cf. Table 1 below) (5). In addition, to better understand how the birth incidence may translate into juvenile or late onset forms, a modeling study by Prosser et al (6) (cf. Table 1) was performed and estimated that screening 4 million babies born each year in the United States would detect 40 cases (range: 13-56) of IOPD , compared with 36 cases (range: 13-56) detected clinically without screening. Newborn screening would also identify each year a total of 94 cases of LOPD that might not become symptomatic for decades. These two studies provide the most recently published estimates for the birth incidence and population prevalence of Pompe disease in the US, and are broadly aligned with other published data worldwide (data not shown).

In Orphanet, Pompe disease is listed as "glycogen storage disease due to acid maltase deficiency" under Orpha number: ORPHA365[1], with an estimated prevalence provided in this database of 1-9 /100,000. In the document "Orphanet Report Series, Rare Diseases Collection, January 2020 Number 1, Prevalence of Rare Diseases: Bibliographic Data Listed in Alphabetical Order of Disease or Group of Diseases"[2], the estimated prevalence is 3.0 /100,000.

In addition, understanding the disease epidemiology may also require an understanding of the disease classification and the survival for each different form of the disease. While this disease classification continues to evolve, as it divides the continuum of disease severity into subjective separate phases based on clinical symptoms, the best estimate on the distribution still comes from Ausems et. al. (7) that showed the Pompe disease phenotypes to be 38%, 4% and 58% for infantile, juvenile, and adult phenotypes, respectively. While this publication refers to a Dutch population, the figure of 1 in 40,000 cited in the publication also corresponds to the frequency calculated in a study in the United States (8). This suggests that the overall disease frequency may be similar in different populations, although the frequency of individual mutations may show local fluctuations. In agreement with literature about the natural progression of the disease, Martiniuk et al. (8) assigned average ages of death of 1 year (without treatment), 15-20 years and 45-60 years for infantile, juvenile and adult-onset phenotypes, respectively.

AGENCY REQUEST FOR INFORMATION ITEM NO. 3:

Provide a proposed maximum dose, with justification, of avalglucosidase alfa for patients with IOPD and LOPD regardless of their weight.

Sanofi response:

There is no maximum total dose of avalglucosidase alfa for a single infusion.

In patients with LOPD, the dose of 20 mg/kg qow demonstrated the optimal benefit-risk profile in the dose ranging study TDR12857, which was confirmed in the Phase 3 double-blind controlled study EFC14028. Based on available data, the recommended dose for patients with LOPD is therefore 20 mg/kg qow.

In patients with IOPD, the doses of 20 mg/kg qow and 40 mg/kg qow demonstrated a positive benefit-risk profile in the ascending dose cohort study, and the highest doses showed additional benefits on some clinical parameters and biomarkers. Both doses demonstrated a favorable safety profile. Therefore, the recommended dose for patients with IOPD is 40 mg/kg qow. The dose may be modified for patients who do not tolerate the recommended dose and for patients who experience safety concerns (eg, severe hypersensitivity, anaphylaxis, or risk of fluid overload).

In the clinical studies with avalglucosidase alfa, the total dose for each infusion was individually calculated based on patient's body weight and dose (mg/kg) as described in the answer to Q1 above, and there was no maximum or cap for the total dose or volume/number of vials per patient. The same approach is recommended in the label submitted for approval, and it is consistent with the approved label for alglucosidase alfa.

Recommendations were made in the clinical studies in both LOPD and IOPD patients to limit the infusion rate because infusion reactions are more likely to occur with higher infusion rates. Infusion should be administered incrementally, as determined by patient response and comfort, over approximately 4 hours for patients with LOPD and 6 hours for patients with IOPD. For patients with IOPD and LOPD, it is recommended that the infusion begins at an initial rate of 1 mg/kg/hour and is gradually increased by 2 mg/kg/hour every 30 minutes if there are no signs of infusion-associated reactions (IARs), until a maximum rate of 7 mg/kg/hour (for patients with LOPD) and 10 mg/kg/hour (for patients with IOPD) is reached. Vital signs should be obtained at each step before increasing the infusion rate. Patients may be pretreated with antihistamines, antipyretics, and/or corticosteroids to prevent or reduce allergic reactions. The same approach is recommended in the label submitted for approval, and it is consistent with the approved label for alglucosidase alfa.

Information request and responses from Genzyme Sanofi received on March 5, 2021:

We acknowledge receipt of your response received on December 10, 2020, in response to our December 2, 2020 information request. In your response you state that preparation of a single dose of Nexviazyme for pediatric patients with IOPD, may require a range of 4 to 26 vials of Nexviazyme with a median of 9 to 10 vials. Moreover, adults and adolescent patients with LOPD would require 8 to 38 vials of Nexviazyme with a median of 13 to 16 vials for preparation of one dose.

As previously communicated to you in the June 3, 2020 proprietary name review granted letter under IND 109569, we maintain our concern regarding your development of a product strength that is incongruent with the dosage and administration of the product; such product strength availability can complicate the calculation, preparation, and administration of a dose leading to medication errors. We are still concerned that the requirement of multiple vials to achieve one dose may be prone to medication preparation and dosing errors. For example, the dose for a 70 kg patient would require 28 vials (dose of 2,800 mg) at the dose of 40 mg/kg.

AGENCY REQUEST FOR INFORMATION ITEM NO. 1:

What are the clinical outcomes and consequences related to overdose and underdose of Nexviazyme? At what dosing intervals are these outcomes evident?

Sanofi response:

Each vial contains 100 mg of avalglucosidase alfa. The number of vials to be reconstituted for an infusion is based on the individual patient's weight and the recommended dose of 20 mg/kg or 40 mg/kg. The dose calculation and the product reconstitution must be made by experienced health care providers. Clear and detailed directions for use are provided in the Prescribing Information in the Dosing and Administration section, consistent with the approach taken for aglucosidase (Lumizyme). The risk of medication error leading to an overdose or an underdose is therefore very limited.

No occurrence of any symptomatic overdose (serious or nonserious) with avalglucosidase alfa has been reported as an AE of special interest (AESI) across all clinical studies in the avalglucosidase alfa development program.

Of note, each vial of avalglucosidase alfa product contains 100 mg of active product, while each vial of the only currently approved ERT for Pompe disease, alglucosidase alfa, product contains 50 mg. Thus, the total number of vials needed for the same dose in Pompe patients is reduced by 50% with avalglucosidase alfa use, potentially leading to improved handling of the preparation of the infusion with avalglucosidase alfa.

Avalglucosidase alfa was well tolerated in mice and monkeys. The no-observed-adverse-effect level (NOAEL) in monkeys following IV administration for 26 weeks was the highest dose tested of 200 mg/kg. No dose higher than 40 mg/kg qow has been evaluated in clinical studies. Patients with IOPD exposed to avalglucosidase alfa 40 mg/kg qow were found to develop higher incidence of IARs and ADA than the 20 mg/kg qow dose, no severe or serious potentially related TEAEs occurred and patients generally did not develop neutralizing antibodies with avalglucosidase alfa regardless of the dose.

Doses of 5 and 10 mg/kg qow were evaluated during the 24 week-study TDR12857. While the effect observed on some efficacy endpoints was less pronounced compared to 20 mg/kg qow, motor function and respiratory function was overall maintained during the course of the study. No unforeseen safety signal was observed with the 2 lowest doses.

No particular clinical outcomes and consequences related to overdose and underdose of Nexviazyme have been observed as part of the clinical development program spanning from the first patient enrolled in study TDR12857 (19 August 2013) to date. Missing multiple successive doses of ERT could have an impact on efficacy outcomes since the underlying glycogen accumulation would not be effectively treated, but no such evidence has emerged during the development program of avalglucosidase alfa.

As the data for avalglucosidase are limited, Sanofi Genzyme conducted a thorough search using the Standardised MedDRA Query of Medication error to determine the individual case reports of medication error with alglucosidase alfa received from worldwide sources from International Birth Date of [redacted] (b) (6) including clinical trial cases, post-marketing cases, and cases from non-interventional studies. Cumulatively, a total of 173 unique case reports were retrieved, containing 175 pertinent events from the MedDRA SMQ Medication errors. Among them, only 2 events reported patients receiving prescribed high doses and 1 event reported a patient receiving a fractionated dose due to an error in calculation.

In the Periodic Benefit Risk Evaluation Report covering the period 29-Sep-2016 through 28-Sep-2019, there were no relevant safety findings on patterns of medication errors and potential medication errors. The review was consistent with known medication errors previously reported for this product. Reports of medication errors and associated Preferred Terms did not impact the safety profile of alglucosidase alfa.

Published literature indicates that doses of alglucosidase alfa higher than the approved dose of 20 mg/kg qow usually are well tolerated, and the safety profile is consistent with the overall safety experience with alglucosidase alfa (1, 2, 3, 4, 5, 6, 7, 8). No new safety or immunogenicity concerns were observed at doses up to 40 mg/kg twice a week for 3 months (7). Most TEAEs observed in the case reports are of mild or moderate severity and unrelated to the use of alglucosidase alfa. While patients receiving the higher dose may develop higher antibody titers and be at higher risk for infusion-associated reactions (IARs), events are mostly mild or moderate and clinically manageable.

In conclusion, the Sponsor proposes that the risk of medication error due to a miscalculation of the number of vials for avalglucosidase alfa is very limited and the handling of the preparation of the infusion with avalglucosidase alfa is improved compared to that of alglucosidase alfa. In case medication error due to a miscalculation would occur, outcomes are expected to be limited to a higher incidence of Anti-drug antibodies and IARs in the case of an overdose, and a risk of impact on efficacy outcomes in the case of an underdose.

AGENCY REQUEST FOR INFORMATION ITEM NO. 2:

Elaborate on the difference between the clinical outcomes associated between a one-time occurrence of an overdose/underdose error verses continuous errors.

Sanofi response:

As detailed in the response to the previous question, no particular clinical outcomes and consequences related to overdose and underdose of Nexviazyme have been observed as part of the clinical development program spanning from the first patient enrolled in study TDR12857 (19 August 2013) to date. The Sponsor reiterates that the dose calculation and the product reconstitution must be made by experienced health care providers, and clear and detailed directions to use are provided in the Dosing and Administration section of the Prescribing Information. The risk of medication error due to a miscalculation in the number of vials is therefore very limited. In case a medication error would occur due to a miscalculation, outcomes are expected to be limited to a higher incidence of ADA and IARs in the case of overdose, and a risk of impact on efficacy outcomes in the case of underdose.

In case clinical outcomes did occur, one could infer that greater consequences would be expected from continuous overdose/underdose errors versus a one-time occurrence. However in clinical practice, use of alglucosidase alfa 40 mg/kg twice a week for 3 months in patients with IOPD (7) and treatment of patients with LOPD with avalglucosidase alfa 5 and 10 mg/kg qow for 6 months did not lead to significant adverse clinical outcomes.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Nexviazyme labels and labeling submitted by Sanofi Genzyme.

- Container label received on September 18, 2020
- Carton labeling received on September 18, 2020
- Prescribing Information (Image not shown) received on september 18, 2020 and February 26, 2021 available from
  \\CDSESUB1\evsprod\bla761194\0002\m1\us\proposedpi.docx

  \\CDSESUB1\evsprod\bla761194\0023\m1\us\annotatedpi.docx

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
03/16/2021 05:23:31 PM

IDALIA E RYCHLIK
03/17/2021 08:12:30 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ORPURM
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Version Date:	March 15, 2021
From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Shetarra Walker, MD, MSCR, Medical Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director DPMH
BLA Number:	761,194
Sponsor:	Genzyme Corporation
Drug:	Avalglucosidase alfa (neo-GAA)
Indication:	Enzyme replacement treatment (ERT) for Pompe Disease, [late (LOPD) (b) (4)
Dosage Form and Route of Administration:	Injection for intravenous (IV) use
Proposed Dose Regimen:	LOPD: 20 mg/kg of body weight, every other week (EOW). (b) (4)
Division Consult Request:	The Division of Rare Diseases and Medical Genetics (DRDMG) request DPMH assistance with labeling this new biologic ERT.

Background

Avalglucosidase alfa is under development for long-term enzyme replacement therapy (ERT) for treatment of patients with Pompe disease (PD; acid α-glucosidase deficiency). On November 19, 2013, the sponsor received orphan designation for avalglucosidase for treatment of patients with Pompe disease.

Two ERTs are currently approved for treatment of patients with PD, Myozyme and Lumizyme. Myozyme (BLA 125,141) is approved for all patients, and infant use was based on improved ventilator-free survival in patients with IOPD compared to an historical control; however, for reasons unrelated to safety, Myozyme is no longer marketed. Lumizyme (BLA 125,291) was originally approved for use in patients 8 years and older (original labeling, May 24, 2010); however, additional pediatric data supported use in all ages (labeling update, August 1, 2014).

The following disease summary is excerpted from the Online Mendelian Inheritance in Man website (OMIM entry #: 232,300).[1] Pompe disease (PD) is caused by an autosomal recessive inborn error of metabolism manifesting as a lysosomal glycogen storage disease which produces multisystem organ dysfunction. Mutations in acid alpha-glucosidase (acid maltase) cause decreased production, or function, or decrease of both production and of functional protein/enzyme.

Classically, three types of PD are described, which differ in severity and age of appearance. These types are known as classic infantile-onset, non-classic infantile-onset, and late-onset. The infantile-onset Pompe disease (IOPD) becomes clinically manifest within a few months of birth and these patients typically produce no functional enzyme. These infants develop muscle weakness (myopathy), poor muscle tone (hypotonia), an enlarged liver (hepatomegaly), and heart defects. Affected infants may also fail to gain weight and grow at the expected rate (failure to thrive) and have breathing problems. If untreated, this form of Pompe disease leads to death from heart failure in the first year of life. Patients with non-classic IOPD produce reduced amounts of functional protein; however, some residual enzyme function remains. These patients typically present later (around 1 year) than patients with classical IOPD and while many symptoms (e.g., muscle weakness and delayed motor milestones) overlap IOPD, cardiac involvement tends to occur later in the disease course. Prior to ERT, these patients only survived through the end of the first or early second decades of life. Late-onset type of Pompe disease (LOPD) typically manifests between the end of the 1st decade up through early adulthood. While generally milder than either classic or non-classic IOPD, most patients will develop progressive muscle weakness of the trunk, limbs, and diaphragm. Prior to ERT, life expectancy for patients with LOPD presenting in childhood and adolescence was approximately 30 years, and life expectancy for patients presenting as adults was approximately 50 years.

Labeling Review

DPMH's labeling recommendations focus on sections 1 (Indications and Usage), 2 (Dosage and Administration), 5 (Warnings and Precautions) and 8.4 (Pediatric Use). Review of the remaining sections [e.g., 6 (Adverse Reactions), and 14 (Clinical Studies)]

[1] OMIM, entry #: 232300; Glycogen Storage Disease II; GSD2; https://www.omim.org/entry/232300. Website accessed January 4, 2021.

is deferred to DRDMG and other consultant disciplines (e.g., Pharmaco-Toxicology and Statistics).

For this review, text which DPMH recommends deleting is noted by ~~strike-out~~, and any text which DPMH recommends adding is noted in **bold red**. The comments below were provided to DRDMG on February 2, 2021. The reader is directed to final approved labeling which may include revised language not addressed in this review.

Reviewer comment: While data are still under review, discussions between the DRDMG, DPMH, and Clinical Pharmacology have established there are adequate data to support the following strategy:

- *Extrapolation of efficacy from adult LOPD to pediatric LOPD is acceptable based on available similar PK data in all Pompe patients (IOPD and LOPD) with body weight as the only significant co-variate. Per Clinical Pharmacology, dosing is weight-based; therefore, extrapolation of efficacy from adults with LOPD to pediatric patients with LOPD is acceptable.*
- *Safety data to support pediatric LOPD can be leveraged from the safety data from ACT14132 (IOPD population between 12 months to 11 years) who are more severely affected, treatment-experienced, and received a higher dose, but who have similar PK data. To further support this argument, Clinical Pharmacology is submitting an information request (IR) to request simulated PK data and analyses to bridge this data into the adolescent LOPD population.*

(b) (4)

[redacted]

The following labeling recommendations are based on the supposition that the data are adequate to support labeling for patients with LOPD.

Boxed Warning

Reviewer comment: Both Myozyme and Lumizyme have boxed warnings for life threatening allergic/hypersensitivity reactions and, for IOPD, cardiac or respiratory failure. Proposed labeling does not include a boxed warning. At the January 6, 2021 midcycle meeting of DRDMG stated that the safety issues in Myozyme and Lumizyme labeling probably apply to all ERTs for IOPD and LOPD, and final labeling will likely include a boxed warning. The language of the boxed warnings in current Myozyme and Lumizyme differ; however, this reviewer concludes the content of the boxed warnings are equivalent. The current boxed warning in Myozyme labeling is presented below for illustrative purposes.

WARNING: ANAPHYLAXIS, SEVERE ALLERGIC AND IMMUNE-MEDIATED REACTIONS AND RISK OF CARDIORESPIRATORY FAILURE

Life-threatening anaphylactic, severe allergic and immune-mediated reactions have been observed in some patients during MYOZYME® infusions. Therefore, appropriate medical support should be readily available when MYOZYME is administered [see Warnings and Precautions (5.1, 5.2)].

Risk of Cardiorespiratory Failure

Patients with compromised cardiac or respiratory function may be at risk for serious acute exacerbation of their cardiac or respiratory compromise due to infusion reactions, and require additional monitoring [see Warnings and Precautions (5.3)].

1 Indication

TRADENAME (avalglucosidase alfa-xxxx) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

Reviewer comment: As noted in section 8.4, pediatric safety and effectiveness were assessed in 19 patients with IOPD, from 1 to 12 years of age, and in 1 adolescent (16 years old) with LOPD. (b) (4) *. If the drug is not approved for use in all ages, DRDMG should consider if the indication statement should have an age-limitation. Also see "Discussion and Recommendations" at the end of this review.*

Because ERT's are intended for lifetime use, DRDMG is considering whether use of modifiers such as "chronic" or "long-term" are necessary for any ERT. Approved labeling will contain the agreed upon term.

2 Dosage and Administration

2.1 Recommended Dosage

Patients with Late-Onset Pompe Disease (LOPD)

The recommended dose of TRADENAME is 20 mg/kg of body weight administered every other week.

(b) (4)

(b) (4)

In the event of anaphylaxis, severe hypersensitivity reaction, or severe infusion-associated reactions (IARs), immediately discontinue administration of TRADENAME and initiate appropriate medical treatment. In the event of mild to moderate hypersensitivity reactions or IARs, the infusion rate may be slowed or temporarily stopped and/or appropriate medical treatment initiated *[see Warnings and Precautions (5.1, 5.2)]*.

Reviewer comment: The above dosages are consistent with how the drug was studied and are acceptable. Review of section 2.3 (Reconstitution, Dilution, and Administration) are deferred to DRDMG and other consultant divisions (e.g. Clinical Pharmacology). ERT's across multiple conditions are labeled for administration in mg/kg at specified rates; both of which are clearly described above. Rate reduction for safety-related reasons (e.g., to reduce the risk of allergic/anaphylactic reactions) is also reflected above and cross-referenced to Warnings and Precautions.

5 Warnings and Precautions

The types and severity of the Warnings and Precautions are similar to those in the most recent Myozyme (BLA 125,141) and Lumizyme (BLA 125,251) labeling supplements, both of which were approved on February 18, 2020. The individual warnings are listed below by subject heading.

5.1 Hypersensitivity Reactions Including Anaphylaxis

5.2 Infusion-Associated Reactions (IARs)

(b) (4)

8.4 Pediatric Use

(b) (4)

Reviewer comment: The above revisions are suggested for clarity because DRDMG confirmed that no patients less 1 year of age were enrolled in clinical studies and because one or more studies in patients less than 1 year of age will be conducted. In response to an information request (IR) on January 21, 2021, (b) (4)

(b) (4)

Discussion and Recommendation

DPMH recommends that section 8.4 not reference use in patients less than 1 year of age because no data are yet available in that age group, and one or more clinical studies are planned for those patients. Furthermore, there are no agreed upon biomarkers for bridging to clinical endpoints [(survival or ventilator free survival in patients with IOPD or superior forced vital capacity (FVC) or 6-minute walk test distance (6MWT-D) from patients with LOPD]. Additionally, while Myozyme, Lumizyme, and the candidate product are presumed to be substantially similar, each product must be supported by its own clinical data.

Summary and Conclusion:

DPMH agrees that from the historical record of the Myozyme and Lumizyme programs it is likely that a candidate product that is effective for treatment of LOPD would likely be effective for treatment of IOPD. However, to date, FDA has not accepted extrapolation of efficacy between LOPD and IOPD and the sponsor presents no biomarker data that might establish such a determination. Therefore, DPMH supports the consensus of the February 1, 2021 internal meeting that lack of clinical data in patients with IOPD from 0 to less than 1 year of age appears to preclude indicating or labeling the drug for these patients prior to establishment of efficacy and safety in clinical studies.

Additionally, since Lumizyme is currently available for treatment of IOPD in patients 0 and older, (b) (4) if efficacy data are lacking does not prevent access to treatment for patients with IOPD. While IOPD is rare, sufficient patients continue to be born such that a controlled study with active comparison to an approved product is ethical and practicable. [Note: Summaries of the basis of approval for ERTs to treat Pompe's disease are presented in the appendix of this document].

Appendix:

Myozyme (IOPD): On April 28, 2006 FDA approved Myozyme for treatment of IOPD based on a clinical trial of 18 infants with IOPD 0 to 7 months at enrollment who did not require ventilatory support (Beitz J, Office Director memo, April 28, 2006). At 52 weeks of treatment all 18 patients were alive and three required ventilatory support. These results were superior to an historical cohort of 61 patients born between 1960 and 2003 of whom only one patient was alive at 18 months. Additional interim data were reported from a study of 21 patients from 3 month to 3.5 years at initial infusion, 16 of whom were ventilator-free at baseline. Of these patients, 10 were ventilator free at 52 weeks, two required ventilatory support, and two died. The ventilator-free survival data supported approval in patients with IOPD. Initial and current labeling, last updated February 18, 2020 does not specifically prohibit use in patients LOPD, however the indication statement is clear that safety and effectiveness in forms of PD other than IOPD has not been adequately studied.

Lumizyme (IOPD and LOPD): On May 24, 2010 FDA approved Lumizyme for treatment of patients with LOPD, ages 8 years and older based on treatment of 90 ERT-naïve patients with LOPD, ages 10 to 70 years in a placebo-controlled trial. Approval was based on superior upright forced vital capacity vs percent predicted and superior 6-minute walk test (6MWT) distance between groups over 78 weeks. Uncontrolled registry data from a group of 15 patients with IOPD treated with an ex-US approved formulation of Lumizyme showed superior survival at 18 months (57%) and 36 months (37%) compared to historical controls at both time points (2%). Although initial labeling stated that the registry data was used to verify 'overall effectiveness' in patients 8 years and older with LOPD, no data were presented in labeling. On August 1, 2014, FDA approved Lumizyme for treatment of patients with IOPD based on data from 57 treatment-naïve patients ages 2 months to 3.5 years at first infusion. Data from one low:high dose-controlled study (20:40 mg QOW), and two open-label studies were submitted. In each study, patients had improved survival and ventilator-free survival compared to historical controls; however, there was no difference in survival or ventilator-free survival in the dose-controlled study.

Candidate product: The sponsor submits Study 1 (EFC14028/COMET), a 49-week, randomized double-blind, active comparator study of 100 treatment-naïve patients with LOPD, age 3 years or older at initial ERT, with an open label follow up (5 years total). Efficacy endpoints were upright % predicted FVC between groups, and 6MWT-D. Study 2 (ACT141) was a 25-week open-label ascending dose cohort study of 22 patients, 1 to < 18 years of age, with IOPD with inadequate response to prior ERT. Efficacy endpoints for Study 2 included composite clinical assessments (GMFM-88, QMFT, Pompe-PEDI, LVMZ score) including eyelid position measurements. None of the endpoints from Study 2 have been used in prior drug development programs, and DRDMG has not conclusively linked any of the candidate endpoints to survival or ventilator free survival in patients with IOPD.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ETHAN D HAUSMAN
03/15/2021 10:57:17 AM

SHETARRA E WALKER
03/15/2021 11:02:07 AM

JOHN J ALEXANDER
03/15/2021 09:24:46 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/2/2021

TO: Division of Rare Diseases and Medical Genetics (DRDMG)
Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine (ORPURM)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761194

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS received an inspection request consult from the Division of Rare Diseases and Medical Genetics on February 4, 2021, for the below analytical site. The requested review goal date was February 18, 2021. The Office of Study Integrity and Surveillance (OSIS) declines to conduct an inspection of the analytical site lised in the consult because the requested review goal date outlined in the consult, does not provide sufficient time for the inspection to be completed and for OSIS to submit an Establishment Inspection Report review to the review division.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	Sanofi US Biomarker and Clinical Bioanalysis Boston	1 Montain Road, Framingham, MA

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLA M FENTY-STEWART
03/03/2021 07:45:44 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Disease, Pediatrics, Urology, and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: February 18, 2021 **Date Consulted:** September 24, 2020

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne Yao, MD, Director, DPMH

To: Jenny Doan, Regulatory Project Manager (RPM)
Division of Rare Diseases and Medical Genetics (DRDMG)

BLA: 761194

Drug: Nexviazyme (avalglucosidase alfa) for injection, for intravenous use

Proposed Indication: For long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

Applicant: Sanofi Genzyme

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- (b) (4) submitted on September 18, 2020.
- DPMH PLLR Review of Lumizyme (alglucosidase alfa) BLA 125291 and Myozyme (alglucosidase alfa) BLA 125141 by Miriam Dinatale, MD, dated May 10, 2019. DARRTS Reference ID: 4431988.
- Applicant's response to information request (IR) submitted on December 8, 2020.
- Applicant's response to IR submitted on February 5, 2021.

Consult Question: DRDMG requests DPMH assistance with the PLLR labeling review for this original BLA.

INTRODUCTION

On September 18, 2020, the applicant, Sanofi Genzyme, submitted an original BLA for Nexviazyme (avalglucosidase alfa) injection. On September 24, 2020, Division of Rare Diseases and Medical Genetics (DRDMG) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy*, *Lactation,* and *Females and Males of Reproductive Potential* subsections.

BACKGROUND

Relevant Regulatory History

- On September 18, 2020, the applicant submitted an original BLA for Nexviazyme (avalglucosidase alfa) with the proposed indication for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).
- On November 10, 2020, the Agency sent the applicant an information request (IR) for an updated review and summary of all available pregnancy and lactation cases with reported exposure to avalglucosidase alfa during the clinical development program.
- On December 8, 2020, the applicant submitted the requested information.
- On January 28, 2021, the Agency sent the applicant and IR to describe their plans for the Pompe Registry to monitor and evaluate the long-term treatment effects of avalglucosidase alfa, including use in pregnant and lactating women.
- On February 5, 2021, the applicant submitted the requested information.

The same applicant (Genzyme) gained FDA approval for Myozyme (alglucosidase alfa) BLA 125141 in 2006 and Lumizyme (alglucosidase alfa) BLA 125291 in 2010 for the same indication (Pompe disease). Nexviazyme is a second-generation enzyme replacement therapy.

Drug Characteristics[1]

- *Mechanism of action:* Pompe disease is an inherited disorder of glycogen metabolism caused by a deficiency of lysosomal enzyme acid α-glucosidase (GAA), which results in intra-lysosomal accumulation of glycogen in various tissues.
    - Avalglucosidase alfa provides an exogenous source of GAA. Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.
- *Dosage and administration:*
    - Patients with Late-Onset Pompe Disease (LOPD): 20 mg/kg of body weight administered every other week.

(b) (4)

- *Warnings and Precautions:* hypersensitivity reactions including anaphylaxis, infusion-associated reactions, immunogenicity, risk of acute cardiorespiratory failure, and cardiac

[1]Integrated Review of Nexviazyme (avalglucosidase alfa) BLA 761194.

arrhythmia and sudden death during general anesthesia for central venous catheter placement.

- *Adverse Reactions:* headache, nausea, pruritus, rash, urticaria, and fatigue.
- *Molecular Weight, Protein Binding, Bioavailability:* not available.
- *Mean plasma elimination half-life:*
  - LOPD patients: 1.6 hours

(b) (4)

Pompe Disease and Pregnancy

Pompe disease is an autosomal recessive lysosomal storage disease characterized by a mutation of the GAA gene that occurs in 1:40,000 births. The clinical spectrum of disease ranges from the severe, rapidly progressive infantile-onset Pompe disease (IOPD), to the slowly progressive, heterogeneous late-onset Pompe disease (LOPD) which manifests later in life (including children and adult presentations).[2] In infants, Pompe disease results in muscular weakness, respiratory insufficiency, cardiac manifestations (cardiomegaly, cardiomyopathy, cardiac failure), and gastrointestinal (GI) manifestations (macroglossia, hepatomegaly, difficulty feeding). In adults, Pompe disease results in slowly progressive limb-girdle and trunk muscle weakness, respiratory insufficiency, and GI manifestations (difficulty chewing or swallowing and macroglossia).

In the U.S., the first enzyme replacement therapies (ERTs) for Pompe disease were approved in 2006 (Myozyme for IOPD; Genzyme) and in 2010 (Lumizyme for LOPD; Genzyme). Lumizyme (alglucosidase alfa) is the current standard of care for both IOPD and LOPD. However, published literature describes the natural history of disease on ERT to plateau or worsen in pulmonary or gross motor function after 2-5 years, suggesting the need to develop second generation therapies for both IOPD and LOPD. Avalglucosidase alfa has a 15-fold increase in mannose-6-phosphate (M6P) moieties compared with alglucosidase alfa, resulting in an increased uptake of avalglucosidase alfa into the diaphragm and other skeletal muscles compared to alglucosidase alfa, according to the applicant.[1]

Data on alglucosidase use in pregnant women with LOPD Pompe disease are available and indicate that pregnancy may cause a worsening of the signs and symptoms of Pompe Disease. In a retrospective cohort study[3], 52 women with adult-onset Pompe disease, who had 125 pregnancies, responded to a questionnaire. The pregnancies took place between 1958 and 2012 with only two pregnancies occurring since alglucosidase became available. Of these 52 women, 10 women with muscle symptoms before and during pregnancy had 17 pregnancies (15 deliveries and 2 miscarriages). Of these 10 women, three women had worsened muscle symptoms during pregnancy, three had symptoms develop during pregnancy and two had worsened symptoms in the postnatal period. 42 women who had 107 pregnancies were asymptomatic. See Table 1 below for details of pregnancy outcomes. The authors concluded that although their data of women with Pompe disease did not demonstrate an increased risk of pregnancy or delivery complications, muscle weakness and respiratory complications might arise or worsen during pregnancy in some women with Pompe disease.

[2] Merritt JK, et al. Lysosomal acid alpha-glucosidase deficiency (Pompe disease, glycogen storage disease II, acid maltase deficiency). UptoDate.com. Topic last updated 12/30/2020.
[3] Karabul, et al. Pregnancy and delivery in women with Pompe disease. Molecular Genetics and Metabolism. 2014. 112: 148-153.

Table 1

Common data regarding pregnancies and pregnancy and birth complications in adult Pompe disease, and data from the German perinatal quality survey (BQS—Bundesauswertung Geburtshilfe 2008), and the Statistical Yearbook 2010 for the Federal Republic of Germany. The patient data was self-reported, and the data from the registry are from patient charts.

	Women with symptoms before and during pregnancy[a]	Women without symptoms before and during pregnancy	p	Reference group[f,h]	p[b]	P[c]
Participants [n]	10	42[d]		n.a.		
Median age at the time of the first pregnancy [years]	24 (16–35)	25 (18–33)	0.62[e]	n.a.		
Median age at the onset of Pompe disease [years]	24 (11–34)	40 (24–64)	0.0009[e]	n.a.		
Pregnancies [n]	17	107		936,854[f]		
Deliveries [n]	15	79	0.24[g]	682,514[f]	0.18[g]	0.91[g]
Miscarriages, n [%]	2/17 (11.8)	20/107 (18.7)	0.73[g]	139,591 (14.9[f])	1[g]	0.28[g]
Abortions, n [%]	0/17 (0)	8/107 (7.5)	0.60[g]	114,296 (12.2[f])	0.25[g]	0.18[g]
Breech presentation, n [%]	0/15 (0)	4/79 (5.1)	1[g]	34,530/669,437 (5.2[h])	1[g]	1[g]
Cesarean section, n [%]	5/15 (33.3)	7/79 (8.9)	0.02[g]	194,676/647,116 (30.1[h])	0.78[g]	<0.001[g]
Forceps, n [%]	1/15 (6.7)	2/79 (2.5)	0.41[g]	4711/669,437 (0.7[h])	0.10[g]	0.11[g]
Vacuum extraction, n [%]	0/15 (0)	4/79 (5.1)	1[g]	34,443/669,437 (5.2[h])	1[g]	1[g]
Median duration of pregnancy [weeks]	40 (34–42)	40 (26–42)	0.60[e]	n.a.		
Preterm birth, n [%][i]	1/15 (6.7)	5/70 (7.1)	1[g]	60,354/669,437 (8.8[h])	1[g]	0.83[g]
Median birth weight [g]	3100 (2500–4000)	3310 (710–4460)	0.49[e]	n.a.		
Low birth weight, n [%][j]	0/15 (0)	10/78 (12.8)	0.36[g]	47,056/669,437 (7.0[h])	0.62[g]	0.07[g]
Preeclampsia, n [%]	0/15 (0)	1/79 (1.3)	1[g]	n.a.		
Bleedings during pregnancy, n [%]	1/15 (6.7)	7/79 (8.9)	1[g]	12,862/669,437 (1.9[h])	0.25[g]	<0.001[g]
Perinatal infant death, n [%]	0/15 (0)	1/79 (1.3)	1[g]	3006/669,437 (0.49[h])	1[g]	0.30[g]
Fetal distress reported, n [%]	3/15 (1320)	5/79 (6.3)	0.31[g]	13,615/667,268 (2.0[h])	0.04[g]	0.02[g]

n.a., not available.

[a] 2 patients had symptoms before their second or third pregnancy. Therefore, their asymptomatic pregnancies are represented in the category "women without symptoms before and during pregnancy". The symptomatic patients are represented in the group of "women with symptoms before or during pregnancy".

[b] Data from women with symptoms during pregnancy were compared with data from the general population.

[c] Data from women without symptoms during pregnancy were compared with data from the general population.

[d] In none of the categories was there a statistically significant difference using Fisher exact test.

[e] Analyzed using T-test for independent samples.

[f] Data from the Statistical Yearbook 2010 for the Federal Republic of Germany.

[g] Analyzed using Fisher's exact test.

[h] Data from the German perinatal quality survey (BQS—Bundesauswertung Geburtshilfe 2008).

[i] Before 37 week gestation.

[j] <2500 g.

In a case report (Cilliers, et al)[4], a 31-year old woman with adult-onset Pompe disease was on a protein rich diet. The patient's disease predominantly affected her respiratory system with a reduction in her vital capacity with a 30% reduction in FVC when supine during pregnancy. At 31 weeks' gestation, the patient developed preeclampsia. She was treated with labetalol and aspirin and remained stable until 37 weeks' gestation when the preeclampsia worsened. She delivered a healthy female infant via Cesarean section and was discharged home four days postpartum.

In another case report (DeVries, J et al)[5], a 40-year old woman with adult-onset Pompe disease continued to receive a non-U.S.-approved alglucosidase alfa product (20mg/kg every other week) during pregnancy and lactation. Before pregnancy, she had moderate limb-girdle weakness and used nocturnal ventilation. During pregnancy, her condition remained stable until the 25th week of pregnancy when she began to experience more difficulties with mobility and respiration (FVC in upright position decreased to 42% and the FVC in the supine position decreased to 25%). The ventilatory frequency and pressure was increased during night-time ventilation. Due to increasing dyspnea, the patient had elective Cesarean section at 37 weeks and 5 days and delivered a healthy male infant. Infant development was normal at one year of age. After delivery, the patient's dyspnea improved, and by one year postpartum, her pulmonary function was better than before pregnancy.

In another case report (Plockinger, U et al)[6], a 38-year old female with adult-onset Pompe disease became pregnant with twins after assisted reproductive treatment. She had restrictive respiratory insufficiency and used non-invasive ventilation at night prior to pregnancy. She was on a non-U.S.-approved alglucosidase alfa product until her pregnancy was confirmed and then asked to stop treatment. At 32 weeks' gestation, the patient developed HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) and delivered two healthy male infants via Cesarean section. The non-U.S.-approved alglucosidase alfa product was resumed after 16 months but discontinued once the patient became pregnant again. She had an uncomplicated second pregnancy and delivered a healthy infant at term. The patient had slight deteriorations in lung function tests during pregnancy with no persistent respiratory dysfunctions noted after the two pregnancies.

Reviewer's Comment
DPMH completed PLLR labeling reviews in 2019 for Sanofi Genzyme's Myozyme (alglucosidase alfa) BLA 125291 and Lumizyme (alglucosidase alfa) BLA 125141. Both of these biological products are enzyme replacement therapies indicated for the treatment of Pompe Disease. A Clinical Considerations for disease-associated maternal and/or embryo-fetal risks was included in subsection 8.1 of labeling for these products which states that untreated Pompe disease has been associated with worsening respiratory and musculoskeletal symptoms in some pregnant women. DPMH recommends including this Clinical Consideration in labeling for Nexviazyme.

[4] Cilliers, et al. Anesthetic management of an obstetric patient with Pompe disease. International Journal of Obstetric Anesthesia. 2008. 17: 170-173.
[5] DeVries, J et al. First experience with enzyme replacement therapy during pregnancy and lactation in Pompe disease. Molecular Genetics and Metabolism. 2011. 1-14: 552-555.
[6] Plockinger, et al. Multiple, Successful Pregnancies in Pompe Disease. JIMD Resp. 2016. 28: 111-118.

REVIEW

PREGNANCY

Nonclinical Experience[1]

Embryo-fetal toxicity studies performed in pregnant mice resulted in maternal toxicity related to an immunologic response (including an anaphylactoid response) and embryo-fetal loss at 1.7 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD. Avalglucosidase alfa did not cross the placenta in mice, therefore, the adverse effects were likely related to the immunologic response in the mothers. Embryo-fetal toxicity studies performed in pregnant rabbits showed no adverse effects on the fetuses at exposure up to (b) (4) times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD. For additional details, refer to the Nonclinical Review by Miyun Tsai-Turton, PhD.

Clinical Trials

Pregnant women were excluded from clinical trials with avalglucosidase alfa. A total of 9 pregnancy exposure cases (5 patient pregnancies and 4 partner pregnancies) have been reported during the clinical development program as of the data cut-off date of November 13, 2020.

Pregnancy outcomes included:

- Patient pregnancies (n=5): spontaneous abortion (n=2), livebirth (n=2), ongoing (n=1).
- Partner pregnancies (n=4): livebirth (n=2), spontaneous abortion (n=1), lost to follow-up (n=1).

No major birth defects were reported. Per protocol, study medication was stopped in female participants as soon as the pregnancy was identified. Thus, avalglucosidase exposure was limited to a maximum of 1 dose during the first trimester in these patients and there are no available data regarding exposure to alvaglucosidase alfa throughout pregnancy.

Applicant's Review of Published Literature

The applicant did not submit a literature review related to avalglucosidase alfa use during pregnancy.

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, Micromedex[7], TERIS[8], Reprotox[9], and Briggs[10] to find relevant articles related to the use of avalglucosidase alfa during pregnancy. Search terms included "avalglucosidase alfa" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," OR "miscarriage." No relevant articles were identified.

[7] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 1//25/21.
[8] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 1/25/21.
[9] Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 1/25/21.
[10] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

LACTATION

Nonclinical Experience

Animal lactation studies have not been conducted with avalglucosidase alfa.

Clinical Trials

Lactating women were excluded from clinical trials with avalglucosidase alfa. The applicant stated no lactation exposures have been reported during the clinical development program as of the data cut-off date of November 13, 2020.

Applicant's Review of Published Literature

The applicant did not submit a literature review related to avalglucosidase alfa use during lactation.

DPMH's Review of Published Literature

This Reviewer performed a search in *Medications and Mother's Milk*[11], LactMed[12], Micromedex[7], Reprotox[9], Briggs[10], PubMed, and Embase to find relevant articles related to the use of avalglucosidase alfa during lactation. Search terms included "avalglucosidase alfa" AND "lactation" OR "breastfeeding." No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience[1]

Intravenous administration of avalglucosidase alfa every other day at doses up to 50 mg/kg (exposure not evaluated) had no adverse effects on fertility in male or female mice. For additional details, refer to the Nonclinical Review by Miyun Tsai-Turton, PhD.

Applicant's Review of Published Literature

The applicant did not submit a literature review related to avalglucosidase alfa effects on fertility.

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, and Reprotox[9] to find relevant articles related to the use of avalglucosidase alfa and effects on fertility. Search terms included "avalglucosidase alfa" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No relevant articles were identified.

DISCUSSION and CONCLUSIONS

Pregnancy

Pregnant women were excluded from clinical trials with avalglucosidase alfa. Available data from the 9 reported cases of inadvertent pregnancy exposure during the clinical development program (5 in female trial participants and 4 in female partners of male trial participants) are

[11] Hale, Thomas (2020) Medication's and Mother's Milk. https://www halesmeds.com Accessed 1/25/21.

[12] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 1/25/21.

insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. DPMH previously reviewed PLLR labeling for Myozyme and Lumizyme in 2019, including available data in women exposed to alglucosidase alfa during pregnancy from the Pompe pregnancy sub-registry, the pharmacovigilance database, and published literature. DPMH concluded the data from post-marketing reports and published case reports on alglucosidase alfa have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Considering the similarities in these two ERTs, DPMH recommends including a statement in subsection 8.1 Risk Summary for avalglucosidase alfa regarding the available pregnancy data for alglucosidase alfa.

Published literature suggest untreated Pompe disease is associated with worsening respiratory and musculoskeletal symptoms in some pregnant women. Therefore, DPMH recommends subsection 8.1 of Nexviazyme labeling include this Clinical Consideration along with a statement in the Risk Summary that continuation of treatment for Pompe disease during pregnancy should be individualized to the pregnant woman.

Pompe disease is a rare condition that affects females of reproductive potential. Thus, exposure to avalglucosidase in pregnant women is anticipated but likely to be rare in the postmarketing setting. Considering available data from inadvertent pregnancy exposure cases during the clinical development program are insufficient to evaluate the safety of avalglucosidase use in pregnant women, it will be important to collect pregnancy safety data post approval. Conducting a pregnancy registry for Nexviazyme is likely not feasible because exposure during pregnancy is anticipated to be low due to the rarity of Pompe disease.

(b) (4)

The Pompe patient registry was issued as a postmarketing commitment (PMC) at the time of approval of Myozyme (alglucosidase alfa) in 2006 and includes a pregnancy and lactation sub-study to monitor outcomes in pregnant women, lactating women, and their offspring. In 2020, Myozyme (alglucosidase alfa) was voluntarily withdrawn and the PMC for the Pompe patient registry was transferred under Lumizyme (alglucosidase alfa). The final study report for this PMC is currently anticipated in September of 2022.

(b) (4)

(b) (4)

During the DPMH review of Lumizyme and Myozyme PLLR labeling in 2019 it was noted that only 8 pregnancy outcomes (from 6 enrolled patients) were available from the Pompe pregnancy sub-registry (from 2006 to 2018); whereas 108 cases had been reported to the applicant's global pharmacovigilance database during the same timeframe.[13] Thus, DPMH agrees with the applicant's assessment that their pharmacovigilance database may be a more robust source of pregnancy safety information. However, DPMH notes that 38/108 (35%) of the reported pregnancy outcomes in the applicant's pharmacovigilance database were unknown which illustrates the important limitations related to the comprehensiveness of the pregnancy data collected through routine pharmacovigilance. Therefore, DPMH recommends issuing a single-arm pregnancy safety study (SPSS) as a postmarketing requirement (PMR) for Nexviazyme to collect pregnancy outcome data following avalglucosidase exposure. See below for DPMH suggested PMR language.

Lactation

Lactating women were excluded from clinical trials with avalglucosidase alfa and no lactation exposures were reported. Overall, there are no available data on the presence of avalglucosidase alfa in human or animal milk, the effects on the breastfed infant, or the effects on milk product. Avalglucosidase alfa is a large glycoprotein that is likely degraded in the infant's gastrointestinal, suggesting systemic exposure by the breastfed infant is likely to be minimal. Therefore, DPMH recommends including the following risk/benefit statement in subsection 8.2 of Nexviazyme labeling: "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Nexviazyme and any potential adverse effects on the breastfed infant from Nexviazyme or from the underlying maternal condition."

DPMH notes subsection 8.2 of PLLR labeling for Myozyme and Lumizyme includes a statement that available published literature suggests the presence of alglucosidase alfa in human milk along with a Clinical Consideration that a lactating woman may consider interrupting breastfeeding and pumping and discarding breastmilk for 24 hours after administration in order to minimize drug exposure to a breastfed infant. However, upon further consideration, DPMH has determined this Clinical Consideration should be removed for Myozyme and Lumizyme PLLR labeling because pump and discard recommendations are not generally recommended for chronically administered drugs. Although the plasma half-life is short (i.e., 1.6 hours for avalglucosidase alfa and 2.3 hours for alglucosidase alfa), there are tissue effects that may affect transfer over time. In addition, it may not be reasonable for the lactating women to pump and discard milk every 2 weeks.

Based on the lack of available data and the anticipated use of avalglucosidase alfa in females of reproductive potential including lactating women, it will also be important to collect safety data in this population postapproval. (b) (4)

[13] DPMH PLLR Review of Lumizyme (alglucosidase alfa) BLA 125291 and Myozyme (alglucosidase alfa) BLA 125141 by Miriam Dinatale, MD, dated May 10, 2019. DARRTS Reference ID: 4431988

(b) (4)

(b) (4)

RECOMMENDATIONS

DPMH recommends the following:

1. PMR language for a single-arm pregnancy safety study and for a clinical lactation study:

    a. Conduct a descriptive study that collects data in women and their offspring who are exposed to Nexviazyme (avalglucosidase alfa) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. This study can be performed either as part of an existing study or as a new study. Outcomes of exposed infants, including growth and development, will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years. (b) (4)

    (b) (4)

2. DPMH updated subsections 8.1 and 8.2 and section 17 of labeling for compliance with the PLLR (see below). DPMH discussed the below labeling recommendations with DRDMG at the labeling meeting on February 9, 2021. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Nexviazyme (avalglucosidase alfa) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8.1 Pregnancy

Risk Summary

Available data from case reports of avalglucosidase alfa use in pregnant women are insufficient to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, available data from post-marketing reports and published case reports on alglucosidase alfa use in pregnant women have not identified a drug-associated risk of adverse pregnancy outcomes. The continuation of treatment for Pompe disease during pregnancy should be individualized to the pregnant woman. Untreated Pompe disease may result in worsening disease symptoms in pregnant women *(see Clinical Considerations).* Embryo-fetal toxicity studies performed in pregnant mice resulted in maternal toxicity related to an

immunologic response (including an anaphylactoid response) and embryo-fetal loss at 1.7 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD. Avalglucosidase alfa did not cross the placenta in mice, therefore, the adverse effects were likely related to the immunologic response in the mothers. Embryo-fetal toxicity studies performed in pregnant rabbits showed no adverse effects on the fetuses at exposure up to (b) (4) times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD *(see Data).*

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Pregnant women exposed to Nexviazyme and healthcare providers should report Nexviazyme exposure by calling XXX-XXX-XXX.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Untreated Pompe disease has been associated with worsening respiratory and musculoskeletal symptoms in some pregnant women.

Data

Animal data

(b) (4)

(b) (4)

Embryo-fetal toxicity studies performed in rabbits at doses of 0, 30, 60, and 100 mg/kg/day administered intravenously once daily on gestational days 6 through 19 resulted in no adverse effects in the fetuses at the highest dose (100 mg/kg/day; (b) (4) times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD). Furthermore, the

administration of TRADENAME intravenously every other day in mice from gestational day 6 through postpartum day 20 did not produce adverse effects in the offspring at the highest dose of 50 mg/kg (maternal exposure not evaluated).

8.2 Lactation

Risk Summary

There are no data on the presence of avalglucosidase alfa in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Nexviazyme and any potential adverse effects on the breastfed child from Nexviazyme or from the underlying maternal condition.

17 PATIENT COUNSELING INFORMATION

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KRISTIE W BAISDEN
02/18/2021 11:09:26 AM

TAMARA N JOHNSON
02/18/2021 12:04:47 PM

LYNNE P YAO
02/19/2021 06:38:49 AM

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 12, 2021

To: Dragos Roman, MD, Acting Director
Division of Gastroenterology and Inborn Errors Products

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Jovita Randall-Thompson, PhD, Pharmacologist
Controlled Substance Staff

Subject: BLA 761194 (IND 109569), Avalglucosidase alfa (neoGAA, GZ402666)
Indication: Treatment of Pompe disease
Dosages: 40 mg/kg of body weight every other week
Formulation: intravenous solution
Sponsor: Genzyme Corporation

Materials Reviewed:

- BLA 761194, 2.7.4 Summary of Clinical Safety, Section 7.6 Drug Abuse Liability Assessment and Section 7.7 Withdrawal and Rebound, August 18, 2020
- BLA 761194, 5.3.5.3 Reports of Analyses of Data from More than One Study, ISS Appendix 2 Analyses of Adverse Events and Deaths, January 15, 2021
- IND 109569, CSS Review, J. Randall-Thompson, DARRTS, January 22, 2020

I. Background

This memorandum is in response to a consult request dated October 15, 2020, from the Division of Rare Diseases and Medical Genetics (DRDMG) pertaining to avalglucosidase alfa. Pursuant to section 351(a) of the Public Health Service Act (PHS Act) and filed in accordance with 21 CFR 601.2(a), Genentech (Sponsor) submitted a Biologics License Application (BLA) for avalglucosidase alfa to the Agency. For BLA 761194, DRDMG requested CSS to review the included abuse-related data and confirm whether the Sponsor addressed all requirements pertaining to the abuse potential assessment of avalglucosidase alfa.

Avalglucosidase alfa is formulated as an intravenous solution (40 mg/kg) and is indicated for pediatric and adult patients with Pompe disease. Avalglucosidase alfa is a recombinant form of

human acid α-glucosidase (rhGAA). It is a modified form of alglucosidase alfa, a long-term enzyme replacement therapy (ERT) currently used to treat Pompe disease and approved under the tradenames Myozyme (BLA 125141, approved April 28, 2006) and Lumizyme (BLA 125291, approved May 24, 2010). Based on its size (120,000 Da), avalglucosidase alfa is not expected to cross the blood brain barrier. The product is administered to patients in a medical facility and given as an injection by medical care personal. Thus, the product's availability is restricted.

(b) (4) to support the position that avalglucosidase did not show a signal of abuse and abuse-related studies were are not needed, additional information was requested from the Sponsor. Specifically, CSS recommended that the Sponsor provide animal toxicology and general behavioral observation results and conduct an assessment of abuse-related adverse events (AEs) and physical dependence and withdrawal symptoms. In response, the Sponsor submitted a Drug Abuse Liability Assessment to the BLA with the aforementioned information (2.7.4 Summary of Clinical Safety, Section 7.6 Drug Abuse Liability Assessment and Section 7.7 Withdrawal and Rebound, August 18, 2020, pages 109 to 110 and 119 to 121).

The following sections provide conclusions and recommendations.

II. Conclusions*

1. There is no need to further evaluate the abuse potential of avalglucosidase alfa, based on the following:

    a. Avalglucosidase alfa targets lysosome in skeletal muscle and causes glycogen to degrade. Avalglucosidase alfa is not chemically or pharmacologically similar to any known drug of abuse that is scheduled.

    b. From an abuse perspective, there were no relevant behavioral and neurobehavioral effects observed in animals following the administration of avalglucosidase alfa (BLA 761194, Study 0658-11097 and 2.6.6 Toxicology Written Summary, Section 8.3.1.).

    c. When administered intravenously to patients with Pompe disease in phase 2 and 3 studies, centrally-mediated adverse events (AEs) potentially related to avalglucosidase alfa were limited and included headache, dizziness, fatigue, tremor and muscle spasms. All other centrally-mediated AEs were reported by less than 2% of patients (BLA 761194, ISS Appendix 2 Analyses of Adverse Events and Deaths, 2.1.2.4 Number (%) of patients with TEAE(s) potentially related to avalglucosidase alfa by primary SOC and PT - Avalglucosidase alfa safety set, page, 224, January 15, 2021).

    d. In summary, the mechanism of action, general nonclinical responses, and associated centrally-mediated AEs shown with avalglucosidase alfa did not present a signal of abuse potential or dependence.

* To be conveyed to Sponsor, if appropriate

III. Recommendations (to the Division)

- Avalglucosidase alfa does not appear to present a potential for abuse and does not warrant scheduling under the Controlled Substances Act.
- The labels for Myozyme and Lumizyme, similar products with the same indication as avalglucosidase alfa do not include Section 9, Drug Abuse and Dependence. Therefore, Section 9 should not be included in the label for avalglucosidase alfa solution for intravenous use.

CSS will not be further involved in the review of this BLA. However, we recommend that the Division contact CSS if the review team identifies any abuse-related concerns associated with the product during the course of their review of this BLA.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOVITA F RANDALL-THOMPSON
02/12/2021 10:06:54 AM

CHAD REISSIG
02/16/2021 08:30:38 AM

DOMINIC CHIAPPERINO
02/16/2021 08:42:50 AM